Fate of aortic bioprostheses: An 18-year experience

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ABSTRACT

Objective: To report our experience in aortic valve replacement with the Mitroflow (Sorin, Vancouver, Canada) aortic bioprosthesis.

Methods: We retrospectively reviewed all patients who underwent aortic valve replacement with a Mitroflow bioprosthesis at our institution from January 1994 to December 2011. No exclusion criteria were retained. Patients were followed yearly. Echocardiography follow-up was performed systematically before the hospital discharge and annually by patients' cardiologists.

Results: Seven hundred twenty-eight patients (mean age, 76 ± 6 years; range, 33–91 years) underwent aortic valve replacement with Mitroflow 12A or LX model and were included in this analysis. 30-day mortality for nonemergent isolated aortic valve replacement was 5.5%. Eight patients (1%) underwent reoperation for structural valve deterioration (SVD) and 30 patients (5.8%) presented echocardiographic signs of SVD. Actuarial freedom from reoperation for SVD was $99\% \pm 0.5\%$ and $95\% \pm 5\%$ at 10 and 15 years. Actuarial freedom from echocardiographic signs of SVD was $77\% \pm 5\%$ and $56\% \pm 11\%$ at 10 and 15 years, respectively. At the univariate analysis, only the mean gradient at discharge ($P = .0200$), the prevalence of size 19 ($P = .0273$), and severe patient–prosthesis mismatch ($P = .0384$) were significantly different in patients developing SVD at follow-up. Freedom from echocardiographic signs of SVD at 8 years were $88\% \pm 4\%$ and $64\% \pm 13\%$ in patients with a Mitroflow > 19 and Mitroflow 19, respectively (log-rank test, $P = .0056$; Wilcoxon test, $P = .0589$).

Conclusions: Overall outcomes were satisfactory. However the risk of early SVD seems higher for the Mitroflow size 19. This size should be reserved for applications when annulus enlargement is risky or there is an anatomic contraindication to sutureless or stentless valve. (J Thorac Cardiovasc Surg 2016;151:754–61)

Freedom from structural valve deterioration (SVD) according to size of prosthesis.

Central Message

Overall outcomes were satisfactory. However the Mitroflow size 19 (Sorin, Vancouver, Canada) seems vulnerable to a higher risk of early degeneration.

Perspective

Mitroflow size 19 (Sorin, Vancouver, Canada) is presently the smallest biological stented valve available on the market. It is broadly employed in small annulus applications. However, Mitroflow size 19 seems vulnerable to a higher risk of early structural valve deterioration. This size should be reserved for applications when the annulus enlargement is risky or when there is an anatomic contraindication to sutureless or stentless valve.

See Editorial Commentary page 762.

Supplemental material is available online.

Important demographic changes are taking place in Western populations. In the European Union, according to Statistical Office of the European Communities,¹ the octogenarian

population has grown from 1.5% in 1960 to 4.8% in 2007 and is expected to reach 7.4% in 2030 (Appendix E1).

As a result of the ageing population, during the past 15 years a higher number of elderly patients have been referred to cardiac surgery for aortic valve replacement. In these patients, biological prostheses are strongly recommended because they offer freedom from anticoagulant treatment and potentially lifelong durability resulting in a better event-free survival when compared with mechanical prostheses. Among the biological aortic valve prostheses currently available, the present design of the Mitroflow valve was introduced 1992 by the model 12A (Sorin, Vancouver, Canada). It is a bovine pericardial prosthesis specifically designed for improved hemodynamic parameters in small aortic annuli. In 2006, the model 12A was replaced by the LX without any modification in the design

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Abbreviations and Acronyms

NSD = nonstructural dysfunction
 PPM = patient–prosthesis mismatch
 SVD = structural valve deterioration

and in the material components, so that model 12A and model LX can be considered the same prosthesis.

The fate of Mitroflow bioprosthesis is unclear. Although published series reported satisfactory hemodynamic parameters and long-term durability,^{2–6} Senage and colleagues⁷ recently reported frequent early structural valve deterioration (SVD) and poor long-term survival after aortic valve replacement with the Mitroflow bioprosthesis and they recommended careful monitoring and urgent redo surgery in patients with severe SVD even in asymptomatic patients.

We report our experience in aortic valve replacement with the Mitroflow aortic bioprosthesis to analyze survival, occurrence of SVD, nonstructural valve dysfunction, and endocarditis after surgery.

MATERIALS AND METHODS

We retrospectively reviewed all patients who underwent aortic valve replacement with the Mitroflow bioprosthesis (12A and LX models) at our institution from January 1994 to December 2011. No exclusion criteria were retained. Morbidity and mortality after the aortic valve replacement were reported according to the latest guidelines.

SVD was defined as a dysfunction or deterioration of the prosthesis (exclusive of thrombosis or infection) determined by reoperation or echocardiographic investigation. At the echocardiographic follow-up, the finding of a mean transprosthetic gradient >40 mm Hg or an aortic regurgitation more than moderate was considered SVD.

Nonstructural dysfunction (NSD) was defined as any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the prosthesis (exclusive of thrombosis or infection).

Diagnosis of endocarditis was based on evidence of abscess, paravalvular leak, pus, vegetation at the reoperation (confirmed as secondary to infection by histologic or bacteriologic studies) or in absence of reoperation by the Duke Criteria for endocarditis.

The follow-up ended in April 2014. Patients were followed either by yearly outpatient visit or by telephone and letter to the referring physician. Echocardiography follow-up was realized systematically before hospital discharge and annually by patients' cardiologists.

Statistical Analysis

Statistical analysis was performed with JMP statistical analysis software (SAS Institute Inc, Cary, NC). Continuous variables are presented as means $\pm$ standard deviation and categorical variables are expressed as frequencies.

For the univariate analysis, continuous variables were compared with the Student *t* test or the Wilcoxon rank-sum test. Categorical variables were compared by means of the χ^2 test or Fisher exact test (2 tailed) if the expected count in any cell was <5.

Completeness of the follow-up was calculated as the ratio of total observed person-time to potential person-time of follow-up to the closing date of the study (C index).⁸ Survival was determined by the Kaplan-Meier method and is expressed as the proportion $\pm$ standard error. Survival was compared by log-rank and Wilcoxon tests.

RESULTS**Populations**

During the study period, 728 patients (mean age, 76 ± 6 years; range, 33–91 years) underwent aortic valve replacement with Mitroflow model 12A or LX and were included in this analysis. Demographic characteristics, patients' history, and operative data are detailed in [Table 1](#). Twenty-six percent of patients were octogenarians and 2% of patients were aged 60 years or younger. Half of patients were in New York Heart Association functional class III or IV. Indication for aortic valve replacement was symptomatic aortic stenosis in 91% of patients (661 patients) and pure aortic regurgitation in 9% of patients (67 patients). In 19 patients (2.5%) the aortic regurgitation was related to endocarditis and in 2 patients (0.3%) to a leaflet prolapse because of type A aortic dissection. Four percent of patients underwent emergency surgery. The left ventricular ejection fraction was unpaired in 20% of patients. Half of patients underwent concomitant procedure. No patients had an enlargement of the aortic annulus. [Table 2](#) details distribution of prosthesis size in our population. The majority of patients received size 21 or size 23, but size 19 was also frequent (10% of patients). Based on the in vivo effective orifice area values given by the manufacturer of the Mitroflow valve, 4% of patients ($n = 30$) had severe patient–prosthesis mismatch (PPM). Severe PPM was observed mostly with sizes 19 and 21 mm ([Table 2](#)).

Survival and Morbidity

Early mortality was 10.3% (75 patients), 12.5% (91 patients), and 13.7% (100 patients) at 30, 60, and 90 days, respectively, after surgery. Thirty-day mortality for nonemergent isolated aortic valve replacement was 5.5% (20 of 359 patients). Cardiogenic shock and multiorgan failure were the main causes of early death ([Table 3](#)).

Two hundred four patients developed at least 1 complication after the surgery. Major bleeding and cardiogenic shock were the most frequent postoperative complications. Less than 3% of patients required pacemaker implantation for permanent atrioventricular block ([Table 3](#)).

There were 230 late deaths. Median survival was 7.4 years. Actuarial survival, including early deaths, was $66\% \pm 2\%$, $33\% \pm 3\%$, and $15\% \pm 7\%$ at 5, 10, and 15 years, respectively, after initial surgery ([Figure 1](#)). Actuarial survival after nonemergent isolated aortic valve replacement was $72\% \pm 2\%$ and $40\% \pm 4.5\%$ at 5 and 10 years, respectively, after initial surgery ([Figure 1](#)).

Reoperation

During the study period (mean follow-up, 4.3 ± 1.3 years; median follow-up, 4 years; range, 0–16.3 years; 3155.81

TABLE 1. Baseline characteristics of the population

Characteristic	Result
Population, n	728
Age (y)	76 ± 6 76 (33-91)
Octogenarians	194 (26)
Age <60 y	11 (1.5)
Men	420 (57)
Body surface area (m ²)	1.81 ± 0.23
Patient history	
High blood pressure	531 (73)
Diabetes	189 (26)
Dyslipidemia	364 (50)
Chronic obstructive pulmonary disease	80 (11)
Tobacco history	65 (9)
New York Heart Association functional class III or IV	320 (44)
Peripheral vascular disease	43 (6)
Atrial fibrillation	145 (20)
Creatine clearance, Modification of Diet in Renal Disease (mL/min)	74 ± 24
Creatine clearance <30 mL/min	22 (3)
Stroke	65 (9)
Redo cardiac surgery	36 (5)
Echocardiographic data	
Left ventricular ejection fraction (%)	62 ± 14
<50%	145 (20)
<35%	29 (4)
Aortic surface area (cm ²)	0.7 ± 0.3
Mean aortic gradient (mm Hg)	43 ± 20
Systolic pulmonary arterial pressure (mm Hg)	35 ± 14
Systolic pulmonary arterial pressure >60 mm Hg	36 (5)
Operative data	
Urgent or emergency surgery	27 (4)
Associated procedure	356 (49)
Associated coronary artery bypass grafting	283 (39)
Cardiopulmonary bypass time (min)	113 ± 53
Aortic crossclamp time (min)	88 ± 36

Values are presented as n, n ± standard deviation, median (range), or n (%).

patient-years; completeness of the follow-up, 721 of 728 [99%]; and C index, 0.90) 18 patients (2.3%) underwent reoperation for SVD, NSD, and endocarditis on the operated valve.

Freedom from Reoperation for SVD

Eight patients (1%) underwent reoperation for SVD (linearized rate, 0.25% patients/year). Seven patients

underwent conventional aortic valve replacement, 1 patient underwent transcatheter aortic valve implantation. No patient died during reoperation. The cause of SVD was leaflet calcification in all patients leading to a pure prosthesis stenosis in 4 patients and stenoin sufficiency in 4 patients. Actuarial freedom from reoperation for SVD was 99% ± 0.5%, 95% ± 5%, and 95% ± 5% at 5, 10, and 15 years, respectively, after initial surgery (Figure 2).

Freedom from Reoperation for NSD

Two patients (0.3%) underwent reoperation for severe paravalvular leak within 6 months after the initial operation. Initial operation was aortic and mitral valve replacement in 1 patient and isolated aortic valve replacement in the other. They had no history of endocarditis and bacteriologic analysis of the prosthesis confirmed the absence of endocarditis. Operative mortality at the reoperation was 50%. Actuarial freedom from reoperation for NSD was 99.8% ± 0.2% at 1, 5, 10, and 15 years, respectively, after the initial operation.

Freedom from Reoperation for Endocarditis on the Operated Valve

Eight patients (1%) underwent reoperation for endocarditis on the operated valve. At the initial operation, no patient presented aortic valve endocarditis. Two patients underwent reoperation within 6 months after the initial operation. Operative mortality at reoperation was 50%. Actuarial freedom from reoperation for endocarditis on an operated valve was 98.7% ± 0.5%, 98% ± 0.5%, and 98% ± 0.5% at 5, 10, and 15 years, respectively, after initial surgery (Figure 3).

Echocardiographic Follow-Up

During the study period (mean follow-up, 5 ± 2.7 years; median follow-up, 4.7 years; range, 0-16.14 years; 2326.2 patient-years; completeness of follow-up, 512 of 655 discharged patients [78%]; and C index, 0.73) 35 patients (6.8%) presented a mean transprosthetic gradient >30 mm Hg and 22 patients (4.3%) presented prosthesis regurgitation more than mild. Among these, 30 patients (5.8%) presented with SVD (linearized rate, 1.28% patients/y): 21 patients had a mean transprosthetic gradient >40 mm Hg, 7 patients presented with prosthetic

TABLE 2. Prosthesis distribution, early postoperative mean gradient, and occurrence of patient-prosthesis mismatch (PPM)

Valve size	n (%)	Mean gradient at discharge (mean mm Hg ± standard deviation)	Mean gradient at follow-up* (mean mm Hg ± standard deviation)	Moderate PPM n (%)	Severe PPM n (%)
19	73 (10)	17 ± 12	19 ± 8	52 (72)	19 (26)
21	238 (32)	14 ± 5	17 ± 7	193 (81)	10 (4)
23	249 (34)	12 ± 5	15 ± 5	166 (66)	1 (0.4)
25	135 (18.5)	10 ± 4	13 ± 6	14 (10)	0
27	33 (4.5)	8 ± 2	13 ± 5	0	0

PPM, Patient-prosthesis mismatch. *Excluding patients with echocardiographic finding of structural valve deterioration.

TABLE 3. Causes of early mortality and early postoperative complications

Variable	Results (n = 728)
Mortality <30 d	75 (10.3)
Causes of early death	
Cardiogenic shock	32 (4.3)
Multiorgan failure	16 (2.2)
Embolism	14 (2)
Stroke	8 (1.1)
Mesenteric ischemia	6 (0.9)
Hemorrhagic shock	7 (0.9)
Sepsis	6 (0.8)
Early complications	204 (28)
Re-exploration for bleeding	115 (15.8)
Cardiogenic shock	58 (7.9)
Extracorporeal membrane oxygenation	15 (2)
Stroke	11 (1.5)
Mesenteric ischemia	8 (1)
Pacemaker implantation	21 (2.8)
Tracheotomy	9 (1.2)
Dialysis	14 (1.9)
Multiorgan failure	22 (3)
Mediastinitis	7 (0.9)
Sepsis	47 (6.4)

Values are presented as n (%).

regurgitation more than moderate without significant prosthesis stenosis, and 2 patients presented with a transprosthetic gradient >40 mm Hg associated with a regurgitation more than moderate. Actuarial freedom from SVD was $97\% \pm 2\%$, $77\% \pm 5\%$, and $56\% \pm 11\%$ at 5, 10, and 15 years, respectively, after initial surgery (Figure 4). Table 2 details mean transprosthetic gradient at the follow-up, according to prosthesis size.

Freedom from SVD was significant different according to severity of PPM (log-rank test, $P = .0023$; Wilcoxon test, $P = .0007$). Freedom from SVD at 8 years was $63\% \pm 16\%$ and $95\% \pm 4\%$ in patients with a severe PPM and no PPM, respectively (Figure 5).

In patients implanted with a Mitroflow size 19, freedom from SVD was significantly lower (log-rank test, $P = .0056$; Wilcoxon test, $P = .0589$). Freedom from SVD at 10 years were $88\% \pm 4\%$ and $64\% \pm 13\%$ in patients with a Mitroflow >19 and Mitroflow 19, respectively (Figure 6). Table 4 details univariate analysis for SVD. Only the mean transprosthetic gradient at discharge ($P = .0200$), the prevalence of size 19 ($P = .0273$), and the prevalence of severe PPM ($P = .0384$) were significantly different in patients developing SVD at the follow-up.

DISCUSSION

The actual design of the Mitroflow was introduced in 1992 with the model 12A. In 2011, Sorin (now LivaNova PLC) released the model DLA introducing an antimicrobial treatment with a solution of 1.2 octanediol. Model DLA was not included in this analysis. Published series reported satisfactory long-term durability with models 12A and LX. When implanted in an elderly population, freedom from reoperation for SVD is estimated between 85% and 92% at 10 years and the linearized rate of reoperation between 0.56% and 1% of patients per year (Table 5). In our experience, during a mean follow-up of 4.3 ± 1.3 years, 1% of patients (8 out of 728) required reoperation for SVD. Freedom from reoperation was $95\% \pm 5\%$ at 10 years with a linearized rate of 0.25% of patients per year. This finding compares well with the

FIGURE 1. Overall survival after aortic valve replacement with the Mitroflow (Sorin, Vancouver, Canada) aortic bioprosthesis, showing nonemergent isolated aortic valve replacement (black line) and the overall population (red line).

FIGURE 2. Freedom from reintervention for structural valve deterioration after aortic valve replacement with Mitroflow (Sorin, Vancouver, Canada) aortic bioprosthesis. SVD, Structural valve deterioration.

published durability of other aortic bioprostheses available in the market. In a recent large series on patients implanted with the Mosaic aortic bioprosthesis (Medtronic Inc, Minneapolis, Minn), Anselmi and colleagues⁹ reported 99% of freedom from reoperation for SVD at 10 years, after a mean follow-up of 8 years.

Ruggieri and colleagues¹⁰ reported 98% of freedom from reoperation for SVD at 10 years in patients implanted with Carpentier-Edwards Supra Annular porcine valve (Edwards Life-sciences, Irvine, Calif), after a mean follow-up of 13 years.

McClure and colleagues¹¹ reported 97% of freedom from reoperation for SVD at 10 years, after Carpentier-Edwards bovine pericardial prosthesis implantation, during a mean follow-up of 8 years.

However, in elderly populations, the analysis of reoperation rate can underestimate the real occurrence of significant SVD at follow-up. In octogenarians, the clinical influence of SVD can be difficult to assess and it may delay the time of surgery. Moreover, because of the high prevalence of comorbidities, the estimated operative risk could be high and play a role in avoidance of redo surgery

FIGURE 3. Freedom from reoperation for endocarditis on operated valve after aortic valve replacement with Mitroflow (Sorin, Vancouver, Canada) aortic bioprosthesis.

FIGURE 4. Freedom from echocardiographic signs of structural valve deterioration (SVD) (ie, mean transprosthetic gradient >40 mm Hg or aortic regurgitation greater than mild) after aortic valve replacement with Mitroflow (Sorin, Vancouver, Canada) aortic bioprosthesis.

in these patients. Echocardiographic follow-up should always be reported to better define the durability of the prosthesis. The Italian study on the Mitroflow postoperative results group⁶ reported the first long-term echocardiographic follow-up on Mitroflow bioprosthesis. Using the same echocardiographic criteria we adopted in our study, they found a freedom from SVD of approximately 90% at 10 years (mean age, 75.3 ± 6.8 years; median follow-up, 5.15 years; 7447 patient-years; and 0.9% of patients per year). Recently, Senage and colleagues⁷ published a

large echocardiographic follow-up on Mitroflow prosthesis. In their series, 6% of patients (39 out of 617) experienced an SVD during the follow-up. A third of SVDs were early and freedom from SVD was 91.6% at 5 years (mean age, 76.1 ± 6.3 years; mean follow-up, 3.8 ± 2 years, patient-years not reported; and patients per year were not reported). In our experience, 5.8% of patients (30 out of 512) presented an echocardiographic sign of SVD during the follow-up but early durability was better: freedom from SVD was $97\% \pm 2\%$ at 5 years and $77\% \pm 5\%$ at 10 years

FIGURE 5. Freedom from echocardiographic signs of structural valve deterioration (SVD) (ie, mean transprosthetic gradient >40 mm Hg or aortic regurgitation greater than mild) after aortic valve replacement with Mitroflow (Sorin, Vancouver, Canada) aortic bioprosthesis, according to severe (black line), moderate (blue line), or no (red line) patient-prosthesis mismatch.

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FIGURE 6. Freedom from echocardiographic signs of structural valve deterioration (SVD) (ie, mean transprosthetic gradient >40 mm Hg or aortic regurgitation greater than mild) after aortic valve replacement with Mitroflow (Sorin, Vancouver, Canada) aortic bioprosthesis, according to prosthesis size 19 (blue line) or size >19 (red line).

(mean follow-up, 5 ± 2.7 years; median follow-up, 4.7 years; range, 0-16.14 years; completeness of follow-up, 512 out of 655 discharged patients [78%]; 2326.2 patient-years; and C index, 0.73).

Our results outline interactions between prosthesis size and long-term durability. These findings are confirmed by Senage and colleagues⁶ and in a large, prospective study reporting a most pronounced trend of increasing gradient over time in the smaller-size valve.² Based on a review of the literature, published series with a lower prevalence of

small prosthesis reported better durability. Asch and colleagues² in their multicenter prospective study reported 2% of prosthesis size 19 and 98% of freedom from SVD at 5 years. On the contrary, Senage and colleagues⁶ reported 22% of prosthesis size 19 and 91% of freedom from SVD at 5 years. Flameng and colleagues¹² extensively investigated interaction between prosthesis size and SVD. They suggested that SVD could be accelerated in small prostheses because the consequent prosthesis mismatch could induce abnormal flow profiles and changes in stress distribution facilitating the calcification process.

The management of a small aortic annulus is still a matter of debate. Enlargement of the annulus has been proposed to reduce the risk of PPM. However, this procedure seems to be associated with a higher mortality rate¹³⁻¹⁵ and the benefit in elderly patients who live a sedentary life is limited.

Mitroflow size 19 is presently the smallest biological stented valve available on the market. Because of its excellent hemodynamic performance (confirmed also by our study), this valve is broadly employed in small annuli when enlargement of the aortic annulus is risky. As a consequence, Mitroflow series when compared with the other valves series, are characterized by a higher prevalence of very small prosthesis that are at risk of accelerated SVD. Comparison of the durability among the valves should take into consideration this potential selection bias.

The model 12A and LX are no more available on the market. They have been replaced by the third generation of Mitroflow, which introduced an antimineralization treatment. Even if overall durability is expected to be

TABLE 4. Univariate analysis for structural valve deterioration (SVD) after aortic valve replacement with Mitroflow (Sorin, Vancouver, Canada) aortic bioprosthesis

Variable	SVD (n = 30)	Not SVD (n = 482)	P value
Demographic characteristic			
Age (y)	74 $\pm$ 6	76 $\pm$ 6	.2096
Age <60 y	1 (3.5)	6 (1)	.4131
Octogenarian	6 (20)	121 (25)	.5207
Men	13 (43)	279 (58)	.1206
Body surface area (m ²)	1.83 $\pm$ 0.2	1.81 $\pm$ 0.2	.5684
Operative data			
Emergency surgery	2 (6.5)	12 (2.5)	.2426
Endocarditis	2 (6.5)	7 (1.5)	.0980
Associated procedures	12 (40)	222 (46)	.5164
Size 19	6 (20)	34 (7)	.0273
Echocardiographic data			
Mean gradient at discharge (mm Hg)	17 $\pm$ 6	12.5 $\pm$ 6	.0200
Moderate patient–prosthesis mismatch	22 (73)	272 (56.5)	.0626
Severe patient–prosthesis mismatch	4 (13)	18 (3.5)	.0384

Values are presented as mean $\pm$ standard deviation or n (%). SVD, Structural valve deterioration.

TABLE 5. Freedom from reoperation for structural valve deterioration according to the recent published series

Series and patients	Mean age (y)	Size 19 (%)	Follow-up (y)	Cumulative follow-up (patient-years)	Reoperation rate (%)	Freedom from reoperation	Linearized rate (% patients/y)
Asch and colleagues (n = 276)	73.6	2.1	4 ± 1.7	1102	2.1	At 5 y: 97.8%	0.56
Jamieson and colleagues (n = 381)	76.4	9.5	5.4 ± 3.4	2048.7	4.2	At 10 y: 85.6% ± 3.8%	0.79
Joshi and colleagues (n = 275)	nr	nr	nr	nr	5.4	At 10 y: 92.5%	nr
Yankah and colleagues (n = 1513)	73.2	13.5	4.07 ± 0.12	6163.5	4.2	At 20 y: 62.3% ± 5.02%	1

nr, Not reported.

better,¹⁶ we believe that because of the very small size, the risk of early degeneration still remains high for the Mitroflow size 19. This size should be reserved for use when annulus enlargement is risky or when there is an anatomic contraindication to use of a sutureless or stentless valve.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: aortic valve, replacement, surgery, complications

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APPENDIX E1. Octogenarian population in the European Union¹

Year	Total population	Age ≥80 y	%
1960	250,624,785	3,821,385	1.52
1970	271,517,342	5,079,602	1.87
1980	284,858,356	6,612,107	2.32
1990	292,673,202	9,721,637	3.32
2000	304,261,341	10,913,818	3.58
2010*	319,586,172	16,188,641	5.06
2020*	330,668,717	20,776,760	6.28
2030*	335,550,827	24,868,286	7.41

Data from 12 European Union countries, including Belgium, Germany (including ex-German Democratic Republic from 1991), Ireland, Greece, Spain, Metropolitan France, Italy, Grand Duchy of Luxembourg, Netherlands, Austria, Portugal, and Finland. *Population projection, convergence year 2150.