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1 Aortic valve repair versus mechanical valve replacement for root aneurysm:

2 The CAVIAAR Multicentric Study

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60 **KEY QUESTION**

61 What is the effect of aortic valve repair versus replacement in patients with
62 dystrophic aortic root aneurysm up to 4 years?

63

64 **KEY FINDINGS**

65 Aortic valve repair reduces the rate of valve-related deaths and major bleeding
66 without increasing risk of re-operation

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68 **TAKE-HOME MESSAGE**

69 This study reinforces medical evidence of the ESC/EACTS guideline recommending
70 aortic valve repair for root aneurysm.

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84 **Abbreviations:** MAVRE (major adverse valve-related events); CAVIAAR (Conservation

85 Aortique Valvulaire dans les Insuffisances Aortiques et les Anévrismes de la Racine

86 aortique) ; AI (aortic insufficiency); IPTW : inverse probability of treatment weighting

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106 **ABSTRACT**

107 **Aims:** Despite growing evidence that aortic valve repair improves long-term patient
108 outcomes and quality of life, aortic valves are mostly replaced. We evaluate the effect of
109 aortic valve repair versus replacement in patients with dystrophic aortic root aneurysm up to
110 4 years.

111 **Methods:** The multicentric CAVIAAR prospective cohort study enrolled 261 patients: 130
112 underwent standardized aortic valve repair (REPAIR) consisting of remodeling root repair
113 with expansible aortic ring annuloplasty, and 131 received mechanical composite valve and
114 graft replacement (REPLACE). Primary outcome was a composite criterion of mortality, re-
115 operation, thromboembolic or major bleeding events, endocarditis or operating site
116 infections, pacemaker implantation and heart failure, analyzed with propensity score-
117 weighted Cox model analysis. Secondary outcomes included Major Adverse Valve Related
118 Events (MAVRE) and components of primary outcome.

119 **Results:** Mean age was 56.1 years, valve was bicuspid in 115 patients (44.7%). Up to 4 years,
120 REPAIR did not significantly differ from REPLACE in terms of primary outcome (HR 0.66 [0.39;
121 1.12]), but showed significantly less valve-related deaths (HR 0.09 [0.02; 0.34]) and major
122 bleeding events (HR 0.37 [0.16; 0.85]) without an increased risk of valve-related re-operation
123 (HR 2.10 [0.64; 6.96]). When accounting for occurrence of multiple events in a single patient,
124 REPAIR group had half the occurrence of MAVRE (RR 0.51 [0.31; 0.86]).

125 **Conclusion:** Although primary outcome did not significantly differ between REPAIR and
126 REPLACE group, the trend is in favor of REPAIR by a significant reduction of valve-related
127 deaths and major bleeding events. Long-term follow-up beyond 4 years is needed to confirm
128 these findings.

129 **Key words:** aortic insufficiency, aortic root aneurysm, aortic valve repair, remodeling

130

131 **INTRODUCTION**

132 Aortic valve repair is now recognized as a good alternative to prosthetic valve
133 replacement with low rate of valve-related events and an improved quality of life compared
134 to valve replacement in monocentric studies **(1–4)**. As a result, the latest 2017 guidelines for
135 heart valve disease recommend a ‘Heart Team discussion’ for selected patients ‘with pliable,
136 non-calcified tricuspid or bicuspid’ aortic valve insufficiency ‘in whom aortic valve repair may
137 be a feasible alternative to valve replacement’ (Class IC indication). Furthermore, aortic valve
138 repair using the re-implantation technique or remodeling with aortic annuloplasty, is
139 recommended in young patients with aortic root dilatation and tricuspid aortic valve (Class
140 IC indication) **(5)**. However, most aortic valves are still replaced. Indeed, according to Euro
141 Heart Survey for Valvular Heart Disease, despite two thirds of cases having a tricuspid or
142 bicuspid dystrophic aortic insufficiency representing suitable candidates for aortic valve
143 repair, only 21.5% had their valve repaired at that time **(6)**. We developed the CAVIAAR
144 technique, a standardized and physiological approach to valve repair, combining the
145 physiological reconstruction of the aortic root according to the Remodeling technique, the
146 systematic assessment of cusp effective height, and the introduction of a calibrated
147 expansible external aortic ring (Extra Aortic Ring, CORONEO Inc, Montreal) **(8–10)**. This
148 multicenter prospective cohort study was designed to investigate if the CAVIAAR
149 standardized valve repair technique was associated with an increased valve-related event
150 free survival compared to mechanical composite valve and graft replacement, in patients
151 undergoing surgery for aortic root aneurysm (bicuspid or tricuspid aortic valves). An early

152 post-operative assessment showed that 30-day mortality was 3.8% (n=5) in both groups
153 (p=1.00) and showed a trend toward fewer major adverse valve-related events (MAVRE) in
154 the REPAIR group **(11)**. This report presents the 4-year results of this prospective cohort
155 study.

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177 **MATERIALS AND METHODS**

178 **Study Overview and Ethics Statement**

179 CAVIAAR (Conservation Aortique Valvulaire dans les Insuffisances Aortiques et les
180 Anévrismes de la Racine aortique) study is a multicenter, prospective cohort study
181 conducted in 22 centers in France, with an inclusion period from May 2007 through October
182 2011. Enrolled patients with aortic root aneurysms were operated either with the CAVIAAR
183 technique consisting of Remodeling root repair and an associated expansible aortic ring
184 (REPAIR), or with a mechanical composite valve and graft replacement (REPLACE). In both
185 groups, consecutive patients were included. Inclusion criteria were adult patients electively
186 operated for an aortic root aneurysm with pliable tricuspid or bicuspid valves regardless of
187 aortic insufficiency (AI) grade, but with an operative indication according to current
188 guidelines [5]. Aortic dissection, redo, urgent operations, patients with aortic stenosis, and
189 patients with formal indication of treatment with anticoagulants (other than mechanical
190 valve) were excluded. All patients provided written informed consent.

191 The protocol was approved by the institutional review board (Committee of
192 Protection of Persons (CPP) of Pitié Salpêtrière University Hospital, Paris, France,
193 authorization n°20-07, given 21/03/2007). The study is registered on the clinicaltrial.gov
194 website as NCT00478803. An independent data and safety monitoring committee provided
195 safety oversight.

196

197 **Study Design**

198 The study was initially a randomized clinical trial. Randomization between the two
199 procedures was done in the operating room, after assessment of aortic valve suitability for
200 repair. Since only 5 patients were recruited within 13 months due to reluctance of the
201 patients and physicians to randomization in this particular context, the study design was
202 revised to a prospective cohort study. In the cohort design, choice of the surgical technique
203 was based on patient, surgeon and referring cardiologist preference. This change allowed a
204 good enrollment rate in the REPAIR group, but in the REPLACE arm, enrollment rate
205 remained low, despite regular reminders sent to investigators. Indeed, centers favoring
206 repair were more prone to include consecutive patients in the study than center favoring
207 valve replacement. Therefore, from those centers, we included the 61 missing patients of
208 the REPLACE group from an ad-hoc historical cohort study. After approval by the institutional
209 review board, all 61 consecutive patients operated with mechanical composite valve and
210 graft operation from May 2007 to October 2011 (inclusion period of the prospective
211 CAVIAAR study) from three of the CAVIAAR study centers were screened for eligibility
212 (exhaustiveness was ensured through systematic screening of the operative room agendas
213 and hospital discharge electronic database (PMSI) for REPLACE surgery). Inclusion criteria
214 were the same as those for the prospective CAVIAAR cohort study and were validated
215 through the pre-operative echo, operative reports, and medical chart review. After October
216 2011, all patients were prospectively followed including the ad-hoc historical cohort of the
217 REPLACE group.

218

219 **Study Procedures**

220 In the REPLACE group, the modified button composite valve and graft Bentall
221 operation was performed using a mechanical aortic valve in all cases. Anticoagulation was
222 performed with vitamin K antagonist aiming an INR range 2-3 as recommended in clinical
223 practice. In the REPAIR group, valve repair procedure was standardized and consisted of
224 combining the Remodeling of the aortic root with subvalvular aortic annuloplasty using an
225 expansible, external aortic ring (Extra Aortic Ring, CORONEO Inc, Montreal) with effective
226 height cusp assessment as previously described (Fig 1) (8–10,12). Aspirin for 3 months post
227 operatively were given after a consensus decision among investigators of the trial, to cover
228 suture anastomosis of coronary ostia.

229 **Outcomes**

230 The primary outcome of the CAVIAAR study is a composite criterion of all-cause
231 mortality, re-operation (including re-exploration for bleeding, tamponade, mediastinitis,
232 need for new permanent pacemaker in the 30-days post-operative period), thromboembolic
233 or major bleeding events, infections (endocarditis or surgical site infections), and heart
234 failure. Events of this outcome have been validated by an adjudication committee involving
235 cardiac surgeons and cardiologists. The secondary endpoints are mortality and the
236 components of the composite primary outcome. To fulfill the AATS/STS/EACTS guidelines for
237 reporting mortality and morbidity after cardiac valve interventions, published in 2008 one
238 year after the beginning of the trial, we added secondarily with the newly recommended
239 MAVRE (Major Adverse Valve Related Events) outcome criterion defined as valve-related
240 mortality (including sudden or unexplained death), valve-related morbidity (need for new
241 permanent pacemaker within 14 days post operatively, thromboembolic or major bleeding
242 events, endocarditis, valve-related re-operation) (13).

243

244 **Data Collection**

245 For all patients, clinical and echographic data were collected pre- and peri-
246 operatively, at discharge, and yearly thereafter. Notifications of all severe adverse events
247 (including all components of the outcome criteria) to the study sponsor was mandatory, and
248 this has been monitored for all patients.

249

250 **Statistical Analysis**

251 The study was sized to determine if valve repair was associated with a 45% decrease
252 in the 3 year-event rate relative to the 32% rate assumed in the REPLACE group. With an
253 80% power and a 5% alpha risk, 123 subjects per group were needed. To account for a 5%
254 loss to follow-up, an enrolment of 130 patients per group was scheduled.

255 Patient characteristics were expressed as means (SD) or medians (interquartile range
256 - IQR) for continuous variables, and as numbers and frequencies for categorical variables.
257 Parametric tests (chi square test for qualitative variables and Student t-test for quantitative
258 variables) were used if the variable was normally distributed. In other cases, we used non-
259 parametric tests (Fisher exact test for qualitative variables and Wilcoxon test for quantitative
260 variables).

261 Treatment groups were assessed for imbalance across demographic, clinical, and
262 echographic data using χ^2 tests (or Fisher's exact tests as appropriate) for categorical
263 variables, and Student's t-test tests (or Wilcoxon tests as appropriate) for continuous
264 variables.

265 To control for a range of potential confounders due to the non- randomized design,
266 an inverse probability of treatment weighting (IPTW) was used and was based on propensity
267 score to construct a weighted cohort of patients, who differed with respect to surgical
268 approach, but were similar with respect to other measured characteristics (14). Each
269 patient's propensity to undergo REPAIR was estimated using a logistic-regression model that
270 included the following observed potential confounding baseline variables: age, gender, Body
271 Mass Index, diabetes, hypertension, NYHA, calendar year of surgery, bicuspid or tricuspid
272 aortic cusps, pre-operative AI grade, and associated cardiac procedures. To assess the
273 balance of measured covariates between treatment groups, we used the absolute
274 standardized difference (ASD) before and after IPTW. An ASD less than 0.1 was considered as
275 evidence of balance.

276 Survival for the different endpoints was described with Kaplan-Meier curves. The
277 hazard ratio for primary and secondary outcomes after REPAIR, as compared with REPLACE,
278 was estimated using the inverse probability of treatment-weighted Cox proportional-
279 hazards models. A post hoc analysis was performed to account for multiple events occurring
280 in a single patient, (thus contributing to patient burden), by estimating the relative risk for
281 primary and secondary outcomes after REPAIR, as compared with REPLACE, with weighted
282 negative binomial regression models (Poisson model extension). In the REPAIR arm, risk
283 factors of high AI grade (> 2) were identified with logistic regression analysis. Influence of
284 aortic cusps type (bicuspid or tricuspid), on valve-related adverse events, was also
285 investigated with logistic regression analysis. A sensitivity analysis was performed by
286 excluding the 61 patients from the retrospective cohort of the REPLACE group.

287 All statistical analyses were performed with R software version 3.5.1 ([https://cran.r-](https://cran.r-project.org/)
288 [project.org/](https://cran.r-project.org/)). Tests were deemed statistically significant at the α level of .05.

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295 RESULTS

296 Patients

297 This article reports results from the analysis of the CAVIAAR study criteria up to 4
298 years after surgery (corresponding to a median [IQR] follow-up of 3.0 [2.7-3.3] years).
299 Follow-up was complete in 92% of patients. The flow chart of the study is presented in
300 Figure 1. 24 patients were intraoperatively excluded because the valve was either too
301 calcified or retracted or with too large fenestrations, and thus not eligible for repair, thus
302 non eligible to the CAVIAAR study. Patient baseline characteristics were previously reported
303 in an early outcomes' publication, with selected demographic and clinical characteristics at
304 baseline summarized in Table 1. Results of logistic-regression model that included observed
305 potential confounding baseline variables used for IPTW is shown in Table S1. 3.8% of
306 patients had Marfan syndrome in the REPAIR group and 4.6% in the REPLACE group ($p=0.77$).
307 Cusp repair was necessary in 63% of patients, with a median of 2 cusps repaired and the rate
308 of cusp repair increased from 43.1% to 83.3% when systematic caliper use was included
309 (after 2009). A second crossclamp was needed in 11 patients in the REPAIR group versus 1

310 patient in the CVG group ($P = .003$) (Table 1). In the REPAIR group, 7 had a bicuspid valve and
311 4 a tricuspid valve. Residual AI of grade 2 or greater dictated re-clamping in 7 patients in the
312 REPAIR group. Schafer's caliper was used in 2 patients. Five patients had cusp repair at the
313 first clamp session. Cusp prolapse was found at reexploration, and the valve was successfully
314 re-repaired in all instances. None of these patients had AI of grade 2 or greater at discharge,
315 but during follow-up 2 patients were reoperated by an aortic valve replacement for severe
316 AI recurrence

317

318 **Endpoints**

319 130 patients had REPAIR and 131 REPLACE. These two groups differed in some
320 Aspects (Table 1: NYHA status, number of cusps). After weighting on the Inverse Probability
321 Weighting Treatment using propensity score estimated in 261 patients, the effect of REPAIR
322 vs REPLACE was estimated in the weighted pseudopopulation, i.e. 2 groups likely to have
323 similar profile and initial severity (Figure S1 and Table S1). Baseline characteristics after IPTW
324 and after sensitivity analysis excluding the 61 patients from the retrospective cohort of the
325 REPLACE group is presented in Table S2 and Figure S2. Up to 4 years, REPAIR did not
326 significantly differ from REPLACE in terms of primary outcome (HR 0.66 IC95% [0.39; 1.12],
327 $p=0.12$, IPTW-weighted) and MAVRE (HR 0.61 IC95% [0.36; 1.06], $p=0.079$, IPTW-weighted),
328 but showed a trend in favor of REPAIR related to significantly less frequent valve related
329 deaths (HR 0.09 IC95% [0.02; 0.34], $p<0.001$, IPTW-weighted) and major bleeding events (HR
330 0.37 IC95% [0.16; 0.85], $p=0.02$, IPTW-weighted) without an increased risk of valve-related
331 re-operation (HR 2.10 IC95% [0.64; 6.96], $p=0.22$, IPTW-weighted) (Figures 2A, 3). After
332 sensitive analysis excluding the 61 patients from the retrospective cohort of the REPLACE

333 group, REPAIR group did not significantly differ from REPLACE group in terms of primary
334 outcome (HR 0.68 IC95% [0.33; 1.38], p=0.283, IPTW-weighted) and MAVRE (HR 0.56 IC95%
335 [0.28; 1.15], p=0.116, IPTW-weighted) up to 4 years.

336 Overall survival was not significantly different between REPAIR (94.12 %; n=8) and
337 REPLACE groups (89.71%; n=14) (HR 0.57 IC95% [0.19; 1.72], p=0.32, IPTW-weighted),
338 however freedom from valve-related death was significantly lower in REPAIR (99.1%, n=1)
339 compared to 94.3% (n=7) in REPLACE (HR 0.09 IC95% [0.02; 0.34], p<0.001, IPTW-weighted).
340 Causes of death in the REPAIR group (n=8) were as follows: 4 cardiac non-valve-related (2
341 heart failures, 1 acute myocardial ischemia, 1 tamponade), 1 cardiac valve-related (1 patient
342 died of mesenteric ischemia after a re-operation for structural valve deterioration at 2
343 years), and 3 not cardiac related. Causes of death in the REPLACE group (n=14) were as
344 follow: 1 cardiac non-valve-related (1 acute myocardial ischemia), 7 cardiac valve-related (3
345 sudden death, 1 endocarditis, and 3 fatal cerebral hemorrhages), and 6 non cardiac related
346 (Figures 2A, 4).

347 When accounting for multiple events occurring in a single patient, REPAIR group
348 showed a not statistically significant trend toward less occurrence of primary outcome (RR
349 0.63 IC95% [0.39; 1.03], p=0.068) and occurrence of MAVRE was significantly less frequent in
350 REPAIR group (RR 0.51 IC95% [0.31; 0.86], p=0.011), mostly related to less frequent major
351 bleeding events (RR 0.34 IC95% [0.16; 0.73], p=0.005) compared to REPLACE (Figures 2B, 4).

352 Major bleeding events occurred exclusively during the peri-operative period for the
353 REPAIR group (re-operation for bleeding or tamponade), and was similar to REPLACE (HR
354 0.57 IC95% [0.25;1.29], p=0.18, IPTW-weighted), while hemorrhagic events during follow-up
355 exclusively occurred in the REPLACE group 8.8% (n=12) versus 0 for REPAIR.

356 Freedom from valve-related re-operation did not statistically differ between both
357 groups (REPAIR 89.8% (n=13) vs REPLACE 93.8 % (n=8); HR 2.10 IC95% [0.64; 6.96], p=0.22,
358 IPTW-weighted). Causes of valve-related re-operations in REPAIR versus REPLACE group
359 showed a trend towards more endocarditis in the REPLACE group (2 vs 6, HR 0.33 IC95%
360 [0.07; 1.49], p=0.15, IPTW-weighted), no difference in non-structural valve deterioration (3
361 vs 2, HR 1.16 IC95% [0.26; 5.18], p=0.84, IPTW-weighted), and more structural valve
362 deterioration in the REPAIR group (8 vs 0, HR). Six out of the 8 re-operations for structural
363 valve deterioration occurred in one center. A sensitive analysis was done excluding this
364 center and freedom from valve-related reoperation did not statistically differ between both
365 groups (HR 0.88 IC95% [0.16; 4.73], p=0.88, IPTW-weighted).

366 Survival free of endocarditis was not different between both group (HR 0.33 IC 95%
367 [0.07; 1.49], p = 0.15, IPTW-weighted) however when accounting for multiple events there
368 was a trend toward more endocarditis in the REPLACE group compare to REPAIR (RR: 0.29 IC
369 95% [0.08; 1.03, p = 0.056).

370

371 **Echocardiographic Analysis**

372 Up to 4 years, 86.4% of patients in the REPAIR group had AI grade 0 or 1, 12.5% had a
373 grade 2, and one patient had a grade 4 (Table 2). No risk factor for occurrence of an AI grade
374 2 was identified. The only risk factor of AI \geq grade 3 was a re-clamping at first operation (HR
375 13.6 IC95% [1.91;96.68], p=0.019) and the pre-operative sinotubular junction diameter (HR
376 1.16 IC95% [1.04;1.29], p=0.005). There was no difference between bicuspid or tricuspid
377 valve in the primary endpoint (HR = 0.95 [0.48,1.90], p=0.886), MAVRE (HR=1.00 [0.47,2.14],
378 p=0.997), nor recurrence of AI grade 2 (HR = 0.40 [0.15,1.09], p=0.055) or 3 (HR = 0.52

379 [0.05,4.96], $p=0.547$). Only one patient with structural valve deterioration died during
380 follow-up 18 months after surgery. This patient died of multiple organ failure.

381 In the REPAIR group, systolo-diastolic expansibility was maintained throughout the
382 pre- and post-operative, as well as the follow-up periods at the aortic annulus level (median
383 5%, 9%, and 5%, respectively), and sinuses of Valsalva level (median 2%, 3%, and 3%,
384 respectively). The aortic ring annuloplasty reduced the native aortic annulus diameter (-
385 20.7%) which remained stable over time. In the REPAIR group, left ventricular end diastolic
386 diameter was reduced throughout the pre- and post-operative (-6.5%), and throughout the
387 post-operative period and up to 4 years (-3%). In the REPLACE group, left ventricular end
388 diastolic diameter was reduced throughout the pre- and post-operative (-13%), and
389 throughout the post-operative period and up to 4 years (-3%).

390 In the REPLACE group, the mean gradient was significantly higher than in the REPAIR
391 group in the post-operative period (median 10 versus 6 mmHg, $p<0.001$, IPTW-weighted),
392 and remained similarly higher up to 4 years (median 9 versus 6 mmHg, $p=0.003$, IPTW-
393 weighted). Similarly, ejection fraction up to 4 years was significantly lower in the REPLACE
394 compared to REPAIR group (median 60% versus 65%, $p=0.004$, IPTW-weighted). No
395 significant difference was noted between the 2 groups regarding left ventricular end
396 diastolic diameter (median 52.5 versus 52, $p=0.811$)

397

398

399 **DISCUSSION**

400 In this prospective cohort study of patients undergoing surgery for dystrophic aortic
401 root aneurysm, the CAVIAAR standardized technique of valve repair was not associated with

402 a significant improvement in the primary outcome up to 4 years (a composite criterion of
403 mortality, re-operation, thromboembolic or major bleeding events, endocarditis or
404 operating site infections, and heart failure), as compared to mechanical composite valve and
405 graft replacement. However, REPAIR group had two third less frequent major bleeding
406 events and ten times less frequent valve-related deaths than REPLACE (Figure 5). Moreover,
407 when we accounted for multiple events occurring in a single patient, REPAIR group had one
408 half the occurrence of MAVRE and two third less frequent major bleeding events than
409 REPLACE. Finally, for most outcomes, the trend was in favor of REPAIR for fewer occurrences
410 which is also combined to a better quality of life without oral anticoagulation daily
411 management and valve noise.

412 Aortic valve sparing operation historical cohort showed excellent survival (90%), and
413 freedom from valve-related re-operation (96%) at 20 years (15). Studies comparing aortic
414 valve sparing versus replacement are mostly single center studies as the recent paper of
415 Ouzounian and al. showing superiority of valve sparing root replacement compared to
416 biological or mechanical composite valve and graft (16). Only one multicentric study was
417 published from the National Marfan Foundation prospective aortic root replacement
418 international registry, enrolling patients operated with various techniques of composite
419 valve graft replacement (85% mechanical, 15% bioprosthetic) or valve-repair procedure
420 (Remodeling and Reimplantation) (1–4,16). Results published at 1 year found no difference
421 in survival, valve-related morbidity, or MAVRE between both groups (17).

422 The main strength of the CAVIAAR cohort comes from being the first multicenter
423 prospective study enrolling a diverse population of patients with dystrophic aortic root
424 aneurysm including Marfan patients, bicuspid or tricuspid valve irrespective of the degree of

425 AI, from a large number of centers, thus providing a good external validation with results up
426 to 4 years. The second strength is to compare two groups undergoing homogenous surgical
427 techniques; that is, either a standardized approach to aortic valve repair (Remodeling root
428 repair with ring annuloplasty) or a mechanical composite valve and graft replacement.
429 Furthermore, multiple events occurring in a single patient were also analyzed as they
430 significantly impact quality of life and patient burden **(18)**. Occurrence of MAVRE taking into
431 account all events in a single patient became significant favoring REPAIR. This finding shows
432 also the limitation of statistical analysis taking into account only single events, while all
433 events contribute to the patient burden.

434 CAVIAAR findings are in coherence with a single center report matching repair and
435 replacement patients, using propensity score analysis and showing an improved survival rate
436 at 9 years in the repair group (87%) versus replacement (60%) ($p=0.007$) [4]. Furthermore,
437 recent meta-analyses on mechanical valve replacement in young patients (< 55 years)
438 showed an early mortality of 6% and an annual late mortality of 2.0%/year after composite
439 mechanical valve and graft replacement and an early mortality of 3.15%, with a late
440 mortality of 1.55%/year for isolated mechanical valve replacement **(19–21)**. A
441 microsimulation to estimate life expectancy based on the age of the patient at surgery for
442 mechanical valve replacement showed a 50% drop in life expectancy post-operatively when
443 compared to general population. In contrast, recent analysis of aortic valve repair for
444 isolated aortic insufficiency showed similar life expectancy compared to the general
445 population **(22)**.

446

447 **Study limitations**

448 The CAVIAAR study also has limitations. First, this is not a randomized controlled trial.
449 Although randomization would have been ideal, attempts to randomize failed due to the
450 reluctance of young patients, referring cardiologists, and surgeons to openly randomize in
451 the operating room between two treatments implying completely different life styles,
452 without taking into consideration patient preference as recommended by the guidelines.
453 Propensity score methods allowed us to take into account the non-randomized scheme and
454 thus limit the indication bias. However, those receiving REPLACE had a greater percentage of
455 patients with BAV and advanced NYHA status compared to the repair group while the repair
456 group also had a higher percentage of those with 0 or 1 preoperative AI compared to the
457 REPAIR group. This may relate to the choice of the surgeons to perform aortic valve repair in
458 selected patients while those receiving REPLACE were a less selected population of historical
459 controls. However, the effect of REPAIR as compared to REPLACE was estimated in the
460 weighted pseudopopulation, to control for known confounders. figure S1 evidences the of
461 covariates included in the propensity score after weighting, including NYHA status and the
462 number of cusps. However, residual confusion cannot be excluded, a randomized controlled
463 trial would have been ideal. Second, in the REPLACE arm, we included 61 patients from an
464 ad-hoc historical cohort study from May 2007 to October 2011 (inclusion period of the
465 prospective CAVIAAR study). However, all these patients were prospectively followed and all
466 eligible to REPAIR in the CAVIAAR study. Third, the primary composite criterion of the study
467 was proposed before current guidelines to report valve-related events defining the MAVRE
468 which is more accurate to evaluate valve event-free survival. Therefore, MAVRE was *a*
469 *posteriori* added to the CAVIAAR study as a secondary endpoint. Forth, some of the
470 complications associated with REPLACE were centered on bleeding, and an INR of 2-3 was

471 recommended in these patients. New mechanical valves with a lower INR target were not
472 considered in the study but may result in a lower bleeding risk in patient undergoing
473 replacement with one of these new mechanical valves. Finally, publication results were
474 delayed compared to the end of follow due to extend time related to the complexity to
475 collect multicentric data including monitoring on site. Ten years outcomes are planned to
476 complete this mid-term follow up of the CAVIAAR trial.

477

478 **Conclusion**

479 Although primary outcome did not significantly differ between REPAIR versus
480 REPLACE group of patients with dystrophic aortic insufficiency, the trend is in favor of
481 REPAIR by a significant reduction of valve-related deaths and major bleeding without an
482 increased risk of re-operation. Occurrence of MAVRE was also significantly reduced when
483 taking into account all events in a single patient. This midterm result is in line with medical
484 evidence guidelines recommending aortic valve repair for root aneurysm. In order to achieve
485 very long follow-up of patient's outcomes, the CAVIAAR cohort was included into the
486 AVIATOR registry from the Heart Valve Society (23).

487

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499

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501 ring. None of the authors have financial disclosure with industry

502 **IRB approval and informed consent statement**: The protocol was approved by the
503 institutional review board (Committee of Protection of Persons (CPP) of Pitié Salpêtrière
504 University Hospital, Paris, France, authorization n°20-07, given 21/03/2007). The study is
505 registered on the clinicaltrial.gov website as NCT00478803. An independent data and safety
506 monitoring committee provided safety oversight. All patients provided written informed
507 consent.

508 **Data availability statement**: all relevant data are within the manuscript

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527 **FIGURE LEGENDS**

528 Central Picture. Kaplan–Meier Survival curve at 4 year-follow-up for freedom from valve-
529 related deaths

530 Figure 1: Flow chart with schematics of both surgical technique arms.

531 Figure 2: Outcomes at 4-year follow-up. A: Inverse probability of treatment–weighted Cox
532 proportional-hazards models (main analysis). B: post hoc analysis to account for multiple
533 events occurring in a single patient, (with weighted negative binomial regression models
534 (Poisson model extension)). In the figures, squares represent point estimates for the hazard
535 ratio (A) or the Relative risk (B) for REPAIR as compared with REPLACE, and horizontal lines
536 indicate the associated 95% confidence intervals.

537 Figure 3: Kaplan–Meier Survival curves at 4 year-follow-up for freedom from composite
538 criterion (A) and freedom from Major Adverse Valve-Related Events (MAVRE) (B)

539 Figure 4: Kaplan–Meier Survival curves at 4 year-follow-up for freedom from valve-related
540 deaths (A) and freedom from bleeding (B)

541 Figure 5: Graphical abstract

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550 TABLES

551 Table 1: Patient Characteristics

	TOTAL (N=261)	REPAIR (N=130)	REPLACE (N=131)	p-value
Age, years, mean±SD (range)	56.1±12.4 (21-82)	56.4 ±12.9 (24-82)	55.7 ±11.9 (21-78)	p=0.65†
Sex Ratio	6.7	5.2	9.1	p=0.13*
BMI (m ²), mean±SD (range)	26.4 ±4.6 (14.8- 43.0)	26.8 ±4.6 (17.0- 43.0)	26.0 ±4.5 (14.8- 40.3)	p=0.18†
Marfan Syndrome	11 (4.2%)	5 (3.8%)	6 (4.6%)	p=0.77*
Bicuspid	115 (44.1%)	43 (33.1%)	72 (55%)	p=0.0001*
NYHA I	139 (53.3%)	84 (64.6%)	55 (42.0%)	p=0.002**

		TOTAL	REPAIR	REPLACE	p-value
		(N=261)	(N=130)	(N=131)	
	II	87 (33.3%)	32 (24.6%)	55 (42.0%)	
	III	30 (11.5%)	13 (10.0%)	17 (13.0%)	
	IV	5 (1.9%)	1 (0.8%)	4 (3.0%)	
Atrial Fibrillation		10 (3.8%)	5 (3.8%)	5 (3.8%)	p=1.0000**
HTA		141 (54.0%)	70 (53.8%)	71 (54.2%)	p=0.95*
AI Grade	0	29 (11.1%)	20 (15.4%)	9 (6.9%)	p=0.0022**
	I	55 (21.1%)	37 (28.5%)	18 (13.7%)	
	II	67 (25.7%)	30 (23.1%)	37 (28.2%)	
	III	67 (25.7%)	26 (20.0%)	41 (31.3%)	
	IV	43 (16.5%)	17 (13.1%)	26 (19.8%)	
Sinuses of Valsalva		50.2±9.0	50.0±9.7	50.5±8.2	p=0.30††
Diameter (mm),		(32-98)	(33-98)	(32-69)	
mean±SD (range)					
Aortic Annulus		27.1 ±2.3	27.9±2.3	26.5±2.1	p<0.0001†
Diameter (Hegar,		(21-40)	(21-40)	(21-32)	
mm) mean±SD					
(range)					

	TOTAL (N=261)	REPAIR (N=130)	REPLACE (N=131)	p-value
Other Cardiac	64 (24.5%)	37 (28.5%)	27 (20.6%)	p=0.14*
Procedures				
ECC Time (min)	156.1±49.2	183.1±38.7	129.1±43.5	p<0.0001†
mean±SD (range)	(65-315)	(114-315)	(65-314)	
AC Time (min)	123.8±38.1	147.7±30.1	99.8±29.2	p<0.0001†
mean±SD (range)	(50-137)	(103-237)	(50-180)	
Second CPB Run	12 (4.6%)	11 (8.5%)	1 (0.8%)	p=0.003*
Reasons				
Hemostasis		3 (2.3%)	1 (0.8%)	
Residual		7 (5.4%)		
AI≥Grade 2				
CABG		2 (1.5%)		
30 days Operative	10 (3.8%)	5 (3.8%)	5 (3.8%)	p=1.00**
Mortality				
Study Composite	54 (20.7%)	24 (18.5%)	30 (22.9%)	p=0.38*
Criterion at 30 Days				
Major Adverse Valve	17 (6.5%)	5 (3.8%)	12 (9.2%)	p=0.08*
Related Events at 30 Days				

552 †Student t test. ††Wilcoxon test. * χ^2 test. **Fisher's exact test.

- 553** Data are presented as number and percentage of patients unless otherwise specified; SD,
- 554** Standard Deviation; NYHA, New York Heart Association; CABG, Coronary Artery Bypass Graft;
- 555** PFO, Patent Foramen Ovale; ECC, ExtraCorporeal Circulation; AC, Aortic Crossclamping; CPB,
- 556** CardioPulmonary Bypass; AI, Aortic Insufficiency

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