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Using national registry data and record linkage to inform post-market

2 surveillance of prosthetic aortic valve models over 15-years

Graeme L. Hickey^{1,2} [Ph.D.], Ben Bridgewater^{2,3} [Ph.D., FRCS (C-Th)], Stuart W. Grant^{2,4} [MB ChB, Ph.D.], John Deanfield² [MB BChir, FRCP], John Parkinson² [Ph.D.], Alan J. Bryan⁵ [MD, FRCS (C-Th)], Malcolm Dalrymple-Hay⁶ [Ph.D., FRCS (C-Th)], Neil Moat⁷ [FRCS], Iain Buchan⁸ [MD, FFPH], Joel Dunning⁹ [Ph.D., FRCS (C-Th)]

8 ¹ University of Liverpool, Department of Biostatistics, Waterhouse Building (Block F), 1-5 Brownlow Street, Liverpool, L69 3GL, UK

10 ² University College London, National Institute for Cardiovascular Outcomes Research (NICOR), 1 St Martin le Grande, London, EC1A 4NP, UK

12 ³ Computer Science Corporation, One Pancras Square, Kings Cross, London, N1C 4AG, UK

14 ⁴ Department of Cardiothoracic Surgery, Lancashire Cardiac Centre, Blackpool Victoria Hospital, Whinney Heys Road, Blackpool, FY3 8NR, UK

16 ⁵ Department of Cardiac Surgery, Bristol Heart Institute, Bristol Royal Infirmary, Bristol, BS2 8HW, UK

⁶ South West Cardiothoracic Centre, Derriford Hospital, Derriford, Plymouth, PL68DH, UK

18 ⁷ Cardiovascular Biomedical Research Unit, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK

20 ⁸ University of Manchester, Manchester Academic Health Science Centre, Centre for Health Informatics, Vaughan House, Portsmouth St, Manchester, M13 9GB, UK

22 ⁹ Department Cardiothoracic Surgery, James Cook University Hospital, Middlesbrough, TS4 3BW, UK

24 * **Corresponding Author:** Mr. Joel Dunning, **Address:** Department Cardiothoracic Surgery, James Cook University Hospital, Middlesbrough, TS4 3BW, UK, **Email:**

26 joeldunning@doctors.org.uk, **Tel:** +44 (0)1642 854612

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30

ABSTRACT

- 32 **Context:** Post-market evidence generation for medical devices is important yet limited for
prosthetic aortic valve devices in the United Kingdom (UK).
- 34 **Objective:** To identify prosthetic aortic valve models that display unexpected patterns of
mortality or re-intervention using routinely collected national registry data and record linkage.
- 36 **Design:** Observational study using the UK National Adult Cardiac Surgery Audit (NACSA)
registry for procedures performed between 1998 and 2013. Valves were classified into series of
38 related models. Outcome tracking was performed using multifaceted record linkage. The median
follow-up was 4.1 years (maximum 15.3 years). Cox proportional hazards regression with
40 random effects (frailty models) were used to model valve effects on the outcomes, with and
without adjustment for (pre-)operative covariates.
- 42 **Setting:** All National Health Service and private hospitals in England and Wales who submit
data to the NACSA registry.
- 44 **Patients and Interventions:** All patients undergoing first-time elective and urgent aortic valve
replacement surgery (\pm coronary artery bypass graft) with a mechanical ($n=10$ series) or
46 biological ($n=15$ series) prosthetic valve from 5 primary suppliers, and satisfying pre-specified
data quality criteria were included ($n=43,782$ biological, $n=11,084$ mechanical).
- 48 **Main Outcome Measures:** Time to all-cause mortality or aortic valve re-intervention (surgical
or trans-catheter). There were 13,104 deaths and 723 re-interventions during follow-up.
- 50 **Results:** Two series of valves were associated with significantly increased hazard of death or re-
intervention were identified: Sorin Biological Series (frailty 1.18 [95%PI: 1.06 to 1.32]) and

52 Sorin Mitroflow series (frailty 1.19 [95%PI: 1.09 to 1.31]). These results were robust to covariate
adjustment, and sensitivity analyses. Three biological valve series were associated with
54 significantly decreased hazard.

Conclusions: Meaningful evidence from the analysis of routinely-collected registry data can
56 inform post-market surveillance of medical devices. Although the findings are associated with a
number of caveats, two specific biological aortic valve series identified in this study may warrant
58 further investigation.

Word count (abstract): 300

60 **Keywords:** Post-market surveillance; prosthetic valves; aortic valves; survival; clinical registry
data

62

INTRODUCTION

64 In recent years there has been a shift in emphasis from establishing device safety and
effectiveness before marketing, to post-market evidence generation and surveillance.¹ The
66 United States Food and Drug Administration (US FDA) system for post-market surveillance has
been found to be in need of strengthening.^{2,3} This need for improved surveillance systems was
68 recently highlighted by the international health scare caused by Poly Implant Prothèse (PIP)
breast implants.⁴ Post-market surveillance systems have historically been reactive rather than
70 proactive in the United Kingdom (UK) as evidenced by concerns over hip prostheses leading to
the UK National Joint Registry being established.⁵

72 Prosthetic heart valves have evolved significantly since the first valve replacement was
performed in 1952. Although there are two main groups of prosthetic heart valve, tissue or
74 mechanical, there are a variety of different valves within these groups. There is a large body of
literature on the long-term reliability of prosthetic heart valves, but these studies, whether
76 randomised trials,⁶ observational,⁷ or case-series,⁸ typically compare a very small number of
valves. Data from systematic benchmarking of long-term performance is not readily available.

78 In the UK, the Heart Valve Registry (UKHVR) was established in 1986 between the
Government's Department of Health and the Society for Cardiothoracic Surgery in Great Britain
80 and Ireland (SCTS).^{9,10} Within 10-years a minimum dataset of clinical variables about heart
valve replacement procedures had been entered for more than 45,000 patients.¹¹ The UKHVR
82 fulfilled an important role: the ability to monitor trends in outcomes by different prosthetic valve
models. It was setup to do this by recording valve model and serial numbers for implanted
84 prosthetic valves, and also by linkage to mortality data, including cause of death, from the Office

for National Statistics (ONS). In 2004, funding was withdrawn due to cost and governance
86 issues, with its functionality partly subsumed by a national adult cardiac surgery register.¹²
Currently, the UK agency responsible for ensuring that medical devices meet applicable
88 standards of safety – the Medicines and Healthcare products Regulatory Agency (MHRA) –
collects data on acute valve failures submitted by healthcare professionals; however, in the
90 absence of a device-specific registry, the opportunity to detect patterns of unexpected outcomes
are limited.

92 Prospective surveillance based on clinical registries that record device-specific
information can identify important signals that passive reporting mechanisms may miss,^{13,14} and
94 there have been calls to move from reactive to proactive monitoring.¹⁴ As a prelude to any
prospective surveillance programme, we present results for a retrospective cross-sectional
96 surveillance analysis of prosthetic valves implanted into patients undergoing aortic valve
replacement (AVR) surgery with or without concomitant coronary artery bypass grafting
98 (CABG) in England and Wales over the past 15-years.

100 MATERIALS AND METHODS

Extraction and preprocessing of aortic valve surgery data

102 A complete extract from the National Adult Cardiac Surgery Audit (NACSA) registry
version 4.1.2), which is run by the National Institute for Cardiovascular Outcomes Research
104 (NICOR; an institute of University College London), was performed on 10th October 2014. This
extract included all adult cardiac surgery procedures performed in UK National Health Service
106 (NHS) hospitals, some private hospitals and some hospitals in the Republic of Ireland. Case
ascertainment of NHS procedure is expected to be high for most of the study period.¹² As part of
108 a wider clinical epidemiological research and quality improvement programme, a regularly
updated suite of ‘data cleaning’ rules developed by specialist clinicians were coded and applied
110 to the raw data (excluding the valve model data) prior to any analysis as summarized in the
Appendix.^{15,16}

112 The initial filtering step was to extract all records corresponding to aortic valve surgery
performed in hospitals located in England and Wales between 1st April 1998 and 31st March
114 2013. Data for one private hospital were removed prior to analysis pending local validation, as
were all data for patients who had more than one record in the registry for the same admission
116 spell. For the purposes of this study, we selected all patients who underwent an AVR ± CABG.
We then excluded all records corresponding to: 1) patients having previous cardiac surgery; 2)
118 suspected incorrectly entered trans-catheter aortic valve implantation (TAVI) procedures (as
identified using a rules-based approach); 3) emergency or salvage procedures; 4) unidentifiable
120 responsible consultant surgeon (as identified by a unique surgeon’s General Medical Council
number in the registry); 5) missing primary outcome data.

122 **Record linkage**

124 To facilitate long-term monitoring of patient and valve status, we performed multiple record linkages for each patient for life status, surgical reoperation, and TAVI as described in the **Appendix**.

126 **Valve model data and data quality**

128 Prostheses are recorded in the NACSA registry in two separate free-text fields: valve name and valve model. There was inconsistency on how each hospital entered these data. An updated suite of data-processing scripts was written to map each recorded name and/or model to a homogenous list of known prosthetic valves using a variety of information sources as described in the **Appendix**. For each record, we attempted to record the valve manufacturer, model, series, and type (mechanical or biological, and xenograft type in the case of biological valves). Here, 'series' refers to a group of valve models from a single manufacturer considered related (See **Table S1** for groupings used). Not all valves could be accurately classified. When valve series was not clear, a subjective decision was made based on expert clinical opinion. Note that manufacturer classification only reflects ownership as of 2015 to the best of our knowledge. Some models have been acquired by manufacturers through business mergers and acquisitions, but are grouped together according to model.

140 Records which were irrelevant or featured gross inconsistencies were excluded, including records that could either not be matched or which were matched to more than one manufacturer, series, or type, or which were matched to >1 model were excluded. Homografts, autografts, rings, valve conduits, two particular model types, off-label procedures, and valves not produced by one of the UK primary suppliers were also excluded (see **Appendix** for details). The 5

144 manufacturers included are Edwards Lifesciences (Irvine, CA, USA), Medtronic Inc.
(Minneapolis, MN, USA), Sorin Group (Milan, Italy), St Jude Medical, Inc. (St. Paul, MN,
146 USA), and Vascutek Ltd. (a Terumo Company, Inchinnan, Scotland, UK).

Study variables

148 For each procedure, data were extracted for administrative factors, patient characteristics,
comorbidities, surgical team, intra-operative factors, and post-operative outcomes. There were
150 few missing clinical data (all >95% complete with the exception of the dichotomous creatinine
variable [5.6% missing], critical preoperative state [7.4% missing], haemodynamics [5.1%
152 missing] and aortic valve pathology [10.1% missing]). Details of study variable definitions and
missing data imputation are given in the **Appendix**.

Study outcomes

The outcome for this study was time from surgery to the first event of death or re-
156 intervention. Patients were censored at the last follow-up time if alive and re-intervention free.
Patients who died in-hospital on the day of surgery were recorded as having a nominal survival
158 time of 0.5 days. Follow-up data, until the point of discharge, were collected by the NACSA
registry and post-discharge survival data were collected by record linkage to the ONS death
160 registry. Re-intervention was defined as surgical reoperation on the aortic valve for any reason or
TAVI. Time-to-re-intervention data was collected by intra- and inter-record linkage as described
162 above.

Statistical analysis

164 Mechanical and biological valves were analyzed separately to avoid confounding by
indication. Valves were compared only at series-level. The Kaplan-Meier estimator was used to
166 construct survival curves for the time-to-event outcome, and compared between valves using
log-rank tests. Multivariable Cox proportional hazards regression models were used to adjust for
168 potential differences with zero-mean valve series-level normally distributed random effects. The
exponentiated random-effects—also known as the shared frailties—act multiplicatively on the
170 baseline hazard rate and therefore have an intuitive translation: frailty terms >1 correspond to
increased hazard for a valve, and those <1 correspond to decreased hazard. Frailties where the
172 corresponding 95% prediction interval lower limit lies above 1 indicate a valve with a
significantly large hazard rate for the outcome. The focus of this study was not the identification
174 of prognostic factors, hence we limit reporting to the frailty effects. For comparison, unadjusted
frailties are also reported. All analyses and data cleaning were performed in R (Version 3.3.1; R
176 Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>). More
detailed description of the statistical analysis is given in the **Appendix**. A number of different
178 sensitivity analyses were performed (reported in the **Appendix**). All inferences remained broadly
consistent.

180

RESULTS

182 From 79,345 AVR ± CABG records with a biological or mechanical prosthesis, a total of
54,866 records were retained for analysis (**Figure 1; Appendix**), from 37 hospitals (including 4
184 private units) and 344 consultant surgeons.

Table S1 lists the valves included, which were grouped into 15 and 10 series of
186 biological and mechanical valves, respectively. **Figure 2** shows an increasing trend in the
implantation rate of biological valves during the study period, stabilising at 86%. **Figure 3** shows
188 the number of valves implanted by time for each series. The distribution of patient age at surgery
(**Figure 4**) indicates homogeneity between the valve-series within type (biological and
190 mechanical), with the exception of greater patient ages for the Medtronic Hall series, Vascutek
Ultracor series, Edwards Lifesciences Mechanical series, and Sorin Sutureless series relative to
192 others of the same type. Plots for logistic EuroSCORE, gender, native valve pathology,
procedure, BMI, valve size, and NYHA grade are shown in **Figures S1-S8**.

194 **Valve outcomes**

During a median follow-up of 4.1 years (maximum follow-up 15.3-years), 13,104 deaths
196 (11,353 biological; 1751 mechanical) were recorded and there were 723 (571 biological; 152
mechanical) re-interventions, (682 were surgical procedures and 41 were TAVIs). Results from
198 the Kaplan-Meier estimator analysis and pathological data for surgical re-interventions are
described in the **Appendix**.

200 After adjustment, the random effects survival model indicated that the Sorin Mitroflow
series (frailty 1.19 [95%PI: 1.09 to 1.31]) and Sorin Biological series (frailty 1.18 [95%PI: 1.06
202 to 1.32]) displayed larger hazard than expected (**Figure 5**). To place the outcomes into

perspective, the 10-year overall freedom from re-intervention or death rates for the 2 valves were
204 33.8% [95%CI: 31.3% to 36.5%] and 41.4% [95%CI: 37.6% to 45.6%], respectively, compared
to the overall average of 47.2% [95%CI: 46.2% to 48.1%] for all non-Sorin biological valves.
206 Although non-significant, the lower 95% PI for the Medtronic ATS-3f series only marginally
crossed the line of unity (frailty 1.21 [95%PI: 1.00 to 1.47]). For mechanical valves, the
208 Medtronic Hall valve had a significantly larger *unadjusted* hazard (unadjusted frailty 1.48
[95%PI: 1.22 to 1.80]). However, after adjustment this was considerably shrunken (adjusted
210 frailty 1.10 [95%PI: 0.97 to 1.24]), reflecting the greater patient age relative to the profile of
other mechanical valves. Additional results are provided in the **Appendix**

212 There were three prosthetic valves with a significant reduction in hazard (**Figure 5**): the
Edwards Lifesciences Perimount series (frailty 0.88 [95%PI: 0.80 to 0.96]), the Edwards
214 Lifesciences Perimount Magna series (frailty 0.88 [95%PI: 0.80 to 0.96]), and the Medtronic
Hancock series (frailty 0.88 [95%PI: 0.78 to 0.98]).

216 A subgroup analysis of all bioprosthesis records performed on or after 1st April 2008
($n=23,834$) showed that the lower 95% prediction interval limit was <1 for every valve after
218 adjustment (see **Appendix**).

220 **DISCUSSION**

222 We analysed a comprehensive clinical registry to measure re-intervention-free survival in
224 a large series of patients undergoing AVR in the UK. Two series of prosthetic aortic valves were
226 associated with significantly increased hazards of death or re-intervention, relative to the
228 population of prosthetic valves implanted in England and Wales from large suppliers. Similarly,
three series of prosthetic valves were associated with decreased hazards. Inferences remained
broadly consistent following covariate adjustment and sensitivity analyses. This study has shown
that routinely-collected clinical registry data can be exploited, in conjunction with multifaceted
record linkage, to perform long-term device surveillance.

230 There is a large literature examining outcomes following different prosthetic AVR
232 implants. Few studies, however, reflect national data. Moreover, the evidence-base is mixed. For
example, some studies have suggested an inferior performance of the Sorin Mitroflow^{17,18}
whereas on the other hand, others have demonstrated long-term durability and haemodynamic
performance.^{19,20}

234 The NHS number—a unique patient identifier—enables record linkage across clinical
registries and other data sources. It would be feasible to exploit this to link across further data
236 sources (e.g. trace readmission from administrative data). In fact, strategic linking of
complementary registries and data sources is a “foundational architectural construct”
238 recommendation of the US Medical Device Registries Task Force.²¹ Furthermore, record-linkage
could be further extended using unique serial numbers of implanted devices (including prosthetic
240 aortic valves) to device manufacturer databases to improve ongoing research, augment clinical
trial follow-up after completion, and to allow traceability in case of serious fault detection. The

242 planned role out by the US FDA of a unique device identification system integrated for use with
electronic health records would allow scalable cross-speciality surveillance.²²

244 We explored outcomes in prosthetic valves cross-sectionally using 15-years of data.
Moving forward, this is not a suitable approach for post-market device surveillance, which
246 should be dynamic, providing regular updates, to achieve superiority over existing passive
reporting mechanisms. It is conceivable that signals of unexpected patterns of outcomes could
248 have been detected earlier on. The Data Extraction and Longitudinal Trend Analysis (DELTA)
network study is a validated example of such a tool, which has utilised propensity score
250 matching and statistical process control methodology to evaluate the safety of high-risk
cardiovascular devices for perioperative binary outcomes.^{13,21,23,24} Similar efforts for post-market
252 surveillance of pharmacological products are also on-going.²⁵ Whilst the methodology applied
here was relatively simplistic, what we have demonstrated is that routinely collected clinical
254 registry data can be leveraged for evaluating performance of medical devices, even when this
was not a primary goal of the data collection programme. With some improvements to the data
256 collection mechanisms, this messy real-world registry, or other registries, data could be analysed
using alternative platforms.

258

LIMITATIONS

260 **Data quality**

262 Research with routinely-collected healthcare data inevitably raises questions over data
264 quality. Many of the data on clinical variables are of high quality, owing to the fact they are used
266 for national governance.^{16,26} Valve-specific data, on the other hand, are not subject to similar
268 quality management. As the valve model data were collected as free-text inputs, more data
quality issues were present than for equivalent clinical information collected using structured
inputs. Data quality is expected to improve in the future, due to increased scrutiny of device
monitoring. Caution must therefore be taken when interpreting the results, as there is potential
for coding errors by the surgeon.

Valve classification

270 Focusing surveillance on a coarsened valve grouping—series—as opposed to valve
models ensured that the maximum number of records would be available for analysis. This
272 decision, whilst allowing us to retain more records for analysis, introduces limitations. Firstly,
different models in a series, including stented and stentless models, or different generations of
274 the same model, might have a variable effect on outcome. For example, the latest generations of
Sorin Mitroflow valves are processed with a phospholipid reduction treatment to mitigate
276 calcification. This might lead to improved performance compared to earlier generations.
Secondly, not all valve series are clearly delineated due to either historical device company
278 purchases/mergers or naming conventions. Similarity in naming means that valves identified to
the series level but not the model level might potentially be misclassified. This is discussed
280 further in the **Appendix**.

Covariate adjustment

282 The adjustment data used in this study derives from a national clinical registry, which is
widely accepted to be superior to administrative data.²⁷ There was no *a priori* expectation of
284 gross selection bias by valve series within valve type, nor was substantial heterogeneity
observed, unlike in some other post-market surveillance studies for cardiovascular devices.¹³
286 However, there has been a shift in patient risk profiles over time,²⁸ which might confound with
market availability of certain valves. We adjusted for baseline risk factors, as well for a number
288 of clinical valve-related variables, and contrasted the change in inference with that of the
unadjusted model. Another potential source of bias stems from the missing data being imputed
290 according to a (gender-stratified) mean/mode approach;²⁹ however, missing data was not
considered substantial. One should also note that the number of random-effects was quite small
292 for a frailty model. Additionally, no adjustment for institutional effects were included, which
could conflate with models implanted.

294 Study outcomes

In some records, patient ID was missing, which can reduce the ability to track patients.
296 Moreover, tracking was terminated at different time points for different endpoints: December-
2012 for TAVI, March-2013 for surgical re-intervention, and July-2013 for survival. Since the
298 focus of the study was on valve surveillance, rather than patient outcomes monitoring, we only
analysed the time to first event. We also note that sample sizes differed substantially between
300 models. This was due to multiple factors, including market availability; some are relatively new
and others have been withdrawn, which might impact on the ability to detect valves that have
302 significantly different event hazards.³⁰ Some newer implanted valves may not yet have sufficient

304 volume to show significantly different outcomes. We have also defined a composite outcome for
analysis, rather than analysing death and re-intervention as a competing risk.³¹ Differences in
outcomes may be attributable to different causes; for example, if a valve migrates it will lead to
306 an increase in re-operation, as was observed with the 3f Enable Aortic Bioprosthesis.³²

The greatest clinical limitations of this study are its relatively short follow-up and lack of
308 other clinical outcomes.³³ The median follow-up time was 4.1-years, however valve failure is
most likely to occur later on, especially in the context of mechanical valves. In fact, only 152
310 surgical re-interventions were observed in the mechanical valve group. Finally, we excluded
patients who had multiple surgical records within a single admission; however, there were only
312 34 such cases satisfying the inclusion criteria for the study.

314 **CONCLUSIONS**

316 The need for such post-marketing surveillance of medical devices was made clear by the
PIP breast implant and other medical device scares,³ yet infrastructure is lacking. We have
shown that a national clinical registry, linked to other routinely-collected data, might be used to
318 inform post-market surveillance programmes. By analysing 15-years of data on AVR
procedures in England and Wales we identified 2 prosthetic valves that may warrant further
320 scrutiny through additional studies. As Taylor noted about valve monitoring nearly 3-decades
ago, “overreaction is as inappropriate as complacency”.³⁴ Given the limitations of the study, the
322 signals shown here should only serve as a hypothesis generating, and not be misinterpreted as
causal effects.

324

STUDY APPROVAL

326 This study was approved by the NICOR NACSA Research Board (study reference 13-
ACS-09), and the need to obtain informed consent from patients was waived as patient
328 identifiable information was either removed or pseudonymised.

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CONFLICTS OF INTEREST

346 BB has received honoraria from Edwards Lifesciences in the last 3-years. JD1 (J.
Dunning) has received proctoring fees from Cardica. MD-H has received honoraria from St. Jude
348 Medical, Edwards Lifesciences and Maquet, and research grants from Edwards Lifesciences and
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350 consultancy for Tendyne (Direct Flow), and speaking from Abbott. All other authors have no
conflicts of interests to declare.

352 **CONTRIBUTORSHIP STATEMENT**

JD1 (J. Dunning) conceived the idea for the study. All co-authors contributed to the
354 development of the study analysis plan. GLH and SWG cleaned the clinical surgical data. GLH,
BB, AJB, MD-H and JD1 cleaned the valve model data. GLH performed the data linkage and
356 statistical analysis. GLH, JD1, BB, SWG, JP and JD2 (J. Deanfield) wrote the manuscript, which
was critically reviewed for intellectual content by all authors. All authors have read and agree to
358 the final version. JD1 acts as guarantor for the manuscript.

DATA SHARING

360 The United Kingdom National Adult Cardiac Surgery Audit registry and the United
Kingdom National TAVI Audit Registry are available to researchers upon application to the
362 National Institute of Cardiovascular Outcomes Research (NICOR), University College London.
Full details on the NICOR data sharing application process are available at
364 <https://www.ucl.ac.uk/nicor/access/application> [last accessed: 16th October 2015].

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454

FIGURE LEGENDS

456 **Figure 1.** Flowchart of study data.

Figure 2. Trend in proportion of biological and mechanical valves implanted over the study
458 period.

Figure 3. Trends in number of valves implanted by valve series over the study period.

460 **Figure 4.** Box-and-whisker plots of patient age at time of surgery stratified by valve series.

Figure 5. Frailty effects (black filled circles) and 95% prediction intervals (black lines) by valve
462 series for time-to-death and time-to-re-intervention as calculated for Cox random effects models
(with and without adjustment for other patient and operative risk factors). Red dashed line
464 denotes 'no effect'.