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Enrico Altiero Giusto

gstncl@unife.it

University of Ferrara

caterina boncompagni

University of Ferrara

Delia Anamaria Bogdan

Sapienza University of Rome

vittorio oteri

University of Catania

milena gabbani

Azienda ULSS 9 Scaligera

paolo pinton

University of Ferrara

carlotta giorgi

University of Ferrara

francesco fiorica

Azienda ULSS 9 Scaligera

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Ten-Year Experience of Cardiotoxicity After Breast Cancer Radiotherapy: a Systematic Review and Meta-Analysis

Enrico Altiero Giusto^{1,2*}, Caterina Boncompagni¹, Delia Anamaria Bogdan³, Vittorio Oteri⁴, Milena Gabbani⁵, Paolo Pinton^{1,6}, Carlotta Giorgi^{1,7*}, Francesco Fiorica^{5,8}

¹ Department of Medical Sciences, Section of Experimental Medicine and Laboratory of Technologies for Advanced Therapy (LTTA), University of Ferrara, 44121 Ferrara, Italy

² Azienda Ospedaliero-Universitaria S. Anna; Via Aldo Moro 8, 44124 Ferrara, Italy

³ Department of Sciences, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy

⁴ Department of Clinical and Experimental Medicine, Endocrinology Section, Garibaldi-Nesima Hospital, University of Catania, Via Palermo, 636, 95122 Catania, Italy

⁵ Department of Clinical Oncology, Section of Radiation Oncology and Nuclear Medicine, AULSS 9 Scaligera, 37122 Verona, Italy

⁶ Maria Cecilia Hospital, GVM Care & Research, 48033, Cotignola (RA), Italy

⁷ Biomedical Research Center, Kansai Medical University, Osaka, Japan

⁸ Department of Clinical Oncology, Section of Medical Oncology, AULSS 9 Scaligera, 37122 Verona, Italy

*Correspondence: gstnci@unife.it (E.A.G.); carlotta.giorgi@unife.it (C.G.) ORCID: <https://orcid.org/0000-0002-2494-7405>

ABSTRACT

Background and aims

Radiotherapy is a cornerstone of breast cancer management, but even modern techniques may entail a residual risk of radiation-induced heart disease. We conducted a systematic review and meta-analysis to quantify the 10-year burden of major adverse cardiac events after breast cancer radiotherapy in relation to mean heart dose and left anterior descending artery dose, and to characterise the associated loss of MACE-free survival using restricted mean measures.

Methods

We systematically searched PubMed, Embase, and Scopus from inception to 05 August 2026. All epidemiological observational studies that investigated cardiotoxicity induced by radiotherapy in breast cancer, including individuals of any ethnicity or sex from all countries and settings that reported Kaplan-Meier or a statistical measure of association or enough data to calculate them, were included. Narrative review, editorial, commentary and letter were excluded. We analysed 24

33 observational studies using both fixed- and restricted-maximum likelihood models; pooled hazard
34 ratios were calculated for Mean Heart Dose, Left Anterior Descending Artery mean dose, and
35 cumulative incidence. Data from Kaplan-Meier curves were extrapolated and derived using
36 Restricted Mean Cumulative Incidence and Restricted Mean Survival Time for incidence burden
37 and probability of free-event time. Methodological quality was assessed with the modified
38 Newcastle-Ottawa Scale, and certainty of evidence was evaluated with the GRADE scale.

39 **Results**

40 The pooled estimate of major acute coronary events related to MHD was HR 1.17 (95% C.I. 1.02-
41 1.34) while MACE related to LAD mean dose were with the fixed effect model HR 1.03 (95% C.I.
42 1.00-1.06), the REML model revealed an increased overall HR for cardiotoxicity following RTp of
43 1.10 (95% C.I. 0.98-1.23) and the cumulative incidence for MACE was 1.15 (95% C.I. 1.00-1.32).
44 In Kaplan Meier curves, the mean cumulative incidence is 23.8% at 10 years, the mean RMCI
45 burden was 0.991 years, the mean RMCI BURDEN TOTAL MACE was 1.168 years, the mean Area
46 of Cumulative Incidence was 116.8, the mean RMST was 8.832 years with an RMST curve area
47 percentage of 88.32%.

48 **Conclusion**

49 This meta-analysis shows that even contemporary breast radiotherapy regimens are associated with
50 a measurable 10-year burden of MACE that scales with MHD and LAD dose. On average, patients
51 lose approximately 1 year of MACE-free life within 10 years after treatment, underscoring the need
52 to minimise cardiac exposure, refine dosimetric constraints for the whole heart and LAD, and
53 integrate cardioprotective strategies into breast cancer radiotherapy planning. The restricted mean
54 framework offers an intuitive, patient-centred metric that may support individualised risk
55 communication and inform future guideline development despite the overall low to moderate
56 certainty of the available evidence

57 **Keywords:** Breast cancer, Radiotherapy, Inflammation, Pathology

58

59 **Abbreviations:** major adverse cardiac events (MACE), radiotherapy-induced heart disease (RIHD),
60 mean heart dose (MHD), left anterior descending artery (LAD), Restricted Mean Cumulative
61 Incidence (RMCI), Restricted Mean Survival Time (RMST), Restricted Mean Cumulative Incidence
62 Burden (RMCI-B), radiotherapy (RT), postoperative radiotherapy (RTp), confidence interval (CI),
63 hazard ratio (HR), Kaplan–Meier (KM)

64

66 ***INTRODUCTION***

67 Radiotherapy is a cornerstone in the management of breast cancer, significantly contributing to
68 local disease control and overall survival. However, robust historical evidence, most notably from
69 the Early Breast Cancer Trialists' Collaborative Group (EBCTCG)[1,2] and the seminal work of
70 Darby et al.[3] has demonstrated that the oncological benefits can be partially offset by an increase
71 in cardiovascular mortality. While toxic effects typically peak after a 10-to-15-year latency period,
72 recent evidence suggests that subclinical damage and early MACE may occur much sooner. This
73 meta-analysis focuses on a 10-year horizon to quantify this early clinical burden. In this context,
74 radiotherapy-induced heart disease[4–7] (RIHD) remains an ongoing clinical challenge. This
75 analysis aims to quantify the incidence of major adverse cardiovascular events (MACE) in relation
76 to key dosimetric parameters: the mean heart dose[8–11] (MHD) and the specific dose received by
77 the left anterior descending (LAD) artery[12–15], which represents the most vulnerable coronary
78 structure due to its anatomical proximity to the target volume in left-sided breast irradiation[16] . A
79 critical methodological issue addressed here is the limited statistical power of current literature,
80 which is often underpowered to define accurate dose-response models, particularly in the low-dose
81 radiation range. This inherent imprecision necessitates a meta-analytic synthesis to clarify the actual
82 risk within modern radiotherapy regimens[17]. Ultimately, this study provides a precise estimate of
83 the years of healthy life lost due to cardiac complications over a 10-year horizon, offering essential
84 tools for treatment personalisation and clinical prevention.

85 The aim of this meta-analysis is to provide a precise estimate of the years of health lost due to
86 cardiac complications over a ten-year horizon, utilising Restricted Mean Survival Time[18–25]
87 (RMST) and Restricted Mean Cumulative Incidence[26] (RMCI) models. This approach could offer
88 essential tools for treatment personalisation and the refinement of clinical prevention strategies.

89

90

91 ***MATERIALS AND METHODS***

92 ***Study Protocol and Standards***

93 The study protocol was registered with PROSPERO (registration number: CRD420261300165). We
94 followed a standardized methodology and reported outcomes according to the Preferred Reporting

95 Items for Systematic Reviews[27] (PRISMA) (Supplementary Table 1) and Meta-analyses of
96 Observational Studies in Epidemiology[28,29] (MOOSE) (Supplementary Table 2)
97 recommendations.

98

99 ***Inclusion/Exclusion Criteria***

100 Two authors (E.A.G. and F.F.) independently screened the literature and reviewed the full texts of
101 potentially eligible articles; any disagreements were resolved through consensus with a third senior
102 author (C.G.). We included epidemiological observational studies-specifically prospective and
103 retrospective cohort or population-based case-control studies-investigating radiotherapy-induced
104 cardiotoxicity in patients treated for breast cancer.

105 To meet the eligibility criteria, studies were required to report: specific radiotherapy techniques or
106 subtypes; dosimetric data for the whole heart or cardiac subvolumes (e.g., LAD), latency periods
107 and clearly defined clinical outcomes (MACE), and effect sizes presented as Hazard Ratios (HR)
108 with 95% confidence intervals (CI), or sufficient raw data to allow for their calculation. Exclusion
109 criteria comprised narrative reviews, editorials, commentaries, and letters.

110 ***Methodological and Statistical Rigour***

111 In accordance with MOOSE guidelines, all methodological items were addressed, including the
112 formulation of the clinical hypothesis, definition of outcomes and exposures, and a comprehensive
113 search strategy. Assessment of confounding factors, study quality and statistical heterogeneity were
114 performed. Results are synthesised through rigorous statistical modelling, with detailed
115 interpretations, study limitations, and clinical implications addressed in the discussion. All
116 information regarding funding, competing interests, and data availability is reported to ensure the
117 reproducibility of the findings.

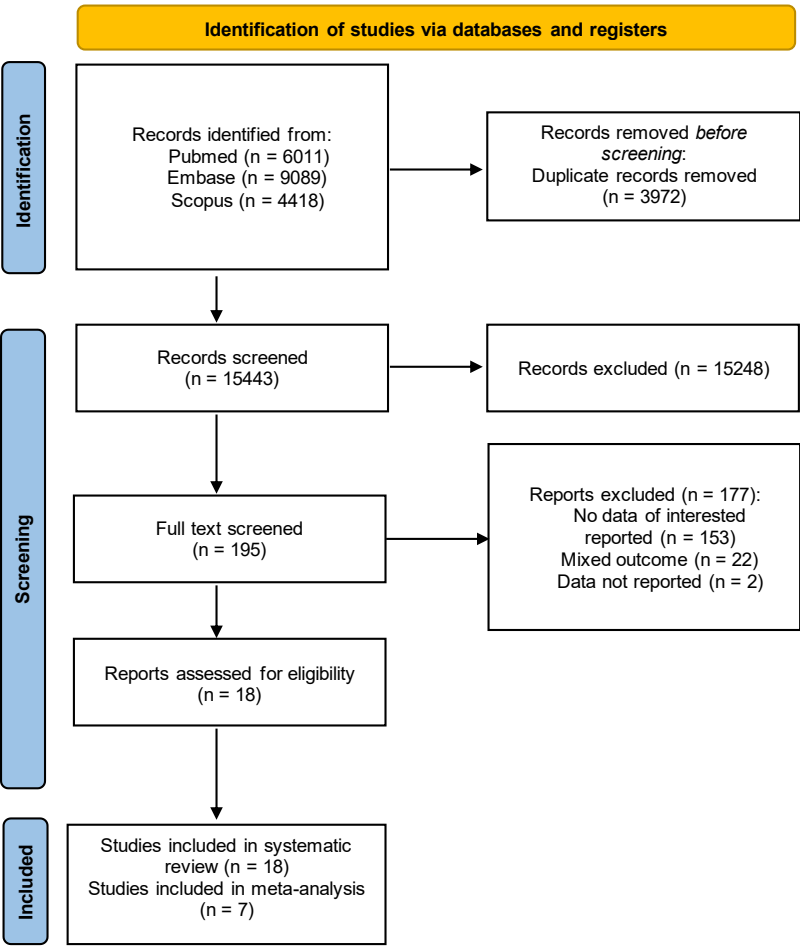
118

119 ***Search Strategy***

120 To identify all relevant manuscripts reporting the risk of cardiotoxicity in patients undergoing
121 radiotherapy for breast cancer, a systematic search was conducted across PubMed, Embase, and
122 Scopus from database inception through 05 August 2026. The search string utilised a combination
123 of Medical Subject Headings (MeSH), exploded terms, and truncated keywords to ensure
124 comprehensive coverage. Specifically, terms related to breast cancer epidemiology and radiation
125 dosimetry were combined using Boolean operators with a free-text search including keywords such

126 as “cancer”, “neoplasm”, “neoplasia”, “tumour”, “survival”, “prognosis” and “carcinoma”. The
 127 search was refined using the “humans” filter to align with the study's focus. To minimise the risk of
 128 missing relevant literature, the reference lists of all included papers and pertinent review articles
 129 were manually screened for additional studies on radiotherapy-induced heart disease. A detailed
 130 summary of the full search strategy is available in the Supplementary Material. Furthermore, a
 131 comprehensive overview of the key findings regarding radiation-induced cardiac toxicity and the
 132 derived dose constraints for the whole heart and specific subvolumes[30,31] (e.g., LAD) is provided
 133 in Table 1.

134 Figure 1. Preferred Reporting Items for Systematic Reviews (PRISMA)



135

136

137 **Data Extraction**

138 Data extraction was made independently by two authors (E.A.G. and F.F.). Divergences were
139 resolved by consensus with P.P. The included papers were reviewed in detail for data on kind of
140 radiotherapy, different doses of RTp, period of treatment, latency of onset of signs and/or symptoms
141 and different systemic or local effects on health, mean left anterior dose[14,15,32] (Mean LAD
142 Dose), mean heart dose (MHD), cumulative incidence of mayor acute coronary events (ACE) and
143 data of Kaplan-Meier curves.

144

145 ***Quality Assessment of the Meta-Analysis Methodology***

146 The methodological quality of the studies was assessed using the modified Newcastle-Ottawa
147 Scale[33] (Modified NOS), a rigorous, accurate, validated, and reliable measurement instrument
148 designed to evaluate cohort and case-control studies. It contains 8 elements and includes ratings for
149 selection, comparability, outcome, and follow-up adequacy. It yields a measurement of
150 methodological quality in 1 of 3 grades: high, moderate, or low. The Revised Cochrane risk-of-bias
151 tool for randomised trials[34,35], ROB 2, was used to evaluate randomised controlled trials. ROB2
152 contains 5 domains: randomisation process, deviations from intended interventions (performance
153 bias), missing outcome Data (attrition bias), measurement of the outcome (detection bias), and
154 selection of the reported result (reporting bias). The overall risk of bias judgement results in low,
155 high and some concerns. The strength of the body of evidence will be assessed through the Grading
156 of Recommendations, Assessment, Development, and Evaluations[36] (GRADE) certainty ratings.
157 Using GRADE guidelines, the examiners investigated the domains for a decrease in certainty: risk
158 of bias, imprecision of true effects, inconsistency of effects, indirectness of outcomes and
159 publication bias (see Supplementary Materials).

160

161 ***Data Analysis***

162 Meta-analysis used both the Restricted Maximum Likelihood[37] (REML) and fixed-effect models,
163 following the Cochrane indications for systematic reviews (Cochrane Handbook for Systematic
164 Reviews of Interventions) to estimate the pooled effect; the heterogeneity and between-study
165 variance components were calculated using a random-effects model. The pooled effect on the risk
166 of developing cardiotoxicity was calculated using hazard ratio (HR); sensitivity analyses and
167 heterogeneity analyses[38] were performed using leave-one-out[39], profile likelihood[40], Baujat
168 plot[41], and Galbraith plot[42,43]. The risk of bias was assessed using funnel plots[44] and
169 Egger's test[45] and trim-and fill analysis[46]. The Kaplan-Meier curves[47–49] for the cumulative

170 incidence of major adverse cardiac events (MACE) were extracted and reported with the mean
171 effect. For effective display, cumulative incidence was reported in histograms with time periods of 5
172 and 10 years. Related analyses were performed to evaluate burden and the cumulative incidence of
173 MACE (%) in the follow-up using the Restricted Mean Cumulative Incidence (RMCI) method and
174 MACE-free probability using the Restricted Mean Survival Time (RMST), Restricted Mean
175 Cumulative Incidence Burden (RMCI-B) method, and RMST[50,51].

176 **Table 1.** Summary of publications focusing on radiation-induced heart toxicity in breast cancer
177 based on several findings, and deduced doses for heart and subvolumes.

178 *Restricted Mean Cumulative Incidence*

179 To overcome the limitations of traditional survival models, we utilised the Restricted Mean
180 Cumulative Incidence (RMCI) as a robust summary measure for comparing cumulative MACE risk.
181 Unlike the Cox proportional hazards model, RMCI does not rely on the proportional hazards
182 assumption and directly quantifies the average time a patient spends in the MACE state within a
183 fixed 10-year horizon.

184 This approach is increasingly recognised in regulatory science; both the Food and Drug
185 Administration (FDA) and the European Medicines Agency (EMA) have acknowledged restricted
186 mean-based endpoints as clinically meaningful, particularly when hazard ratios vary over time or
187 when capturing the full trajectory of the incidence curve is paramount. The RMCI inherently
188 incorporates censoring by utilising observed data directly, providing a more stable estimate in the
189 presence of competing risks.[19]

190 Mathematically, the RMCI over a time period τ (set at 10 years for this study) is defined as the
191 integral of the cumulative incidence function:

$$192 \quad \text{RMCI}(\tau) = 1/\tau \int_0^t F(t) dt$$

193 Where $F(t)$ is the cumulative incidence $\text{MACE}(t)$ as probability of having at least one MACE in
194 period t (0-10 years) and τ as 10 years (time period).

195 The cumulative incidence MACE at 10y (%) can also be defined as

$$196 \quad F(10) = 1 - S(10)$$

197 Where $S(10)$ is the probability of being MACE-free at 10 years, calculated using the product-limit
198 estimator:

$$S(10) = \prod_{t_i \leq 10} \left(1 - \frac{d_i}{n_i}\right)$$

with t_i : Distinct observed MACE event times, d_i : Number of MACE events exactly at t_i , n_i : Patients at risk just before t_i (not censored), $S(10)$: Probability of being MACE-free at 10 years (survival curve value) and $F(10)$: Probability of at least one MACE within 10 years ($1 - S(10)$).

By integrating these discrete points, RMCI captures the clinical burden (expressed in %*years), offering a more intuitive and statistically rigorous interpretation of radiotherapy-induced cardiotoxicity than traditional point estimates.

Area Cumulative Incidence (years*%100)

For the cumulative exposition to the risk, the measure of area indicates cumulative risk over 10 years. Area was calculated as

$$\int_0^{10} \text{CumInc_MACE}(t) \times 100 \, dt$$

Where $\text{CumInc_MACE}(t)$ = is the probability of having at least one MACE in period t (0-10 years).

The multiplication by 100 is for percentage. The measure unit is mean risk for total time.

The method to calculate the Area of cumulative incidence was the exact trapezium method defined as

$$[(0+5y)/2 \times 5] + [(5y+10y)/2 \times 5] \times 100$$

on discrete data. Area trapezium is mean risk $(0\% + 5y\%)/2$ multiply for the time period bases of year.

Restricted Mean Cumulative Incidence Total Burden

RMCI burden[52] is the total years lost for MACE. It is defined as:

$$\text{RMCI Burden} = \text{Area of cumulative incidence}/100$$

223 RMCI burden is the total years lost for MACE. It is defined as:

224 ***Restricted Mean Cumulative Incidence Burden in 10 years***

225 RMCI's 10-year burden is the number of years lost to MACE over 10 years. It is defined:

226
$$\text{RMCI Burden}(\tau=10)=\int_0^{10}F(t)dt$$

227 ***Restricted Mean Survival Time***

228 The Restricted Mean Survival Time estimates the free years from MACE.

229
$$RMST=10-\int_0^{10}F(t)dt$$

230

231 Where F(t) is the cumulative incidence MACE(t).

232 ***Area Restricted Mean Survival Time***

233 The Kaplan-Meier curve for the Restricted Mean Free Disease Time estimates the percentage of
234 time disease-free.

235 It is defined as:

236
$$\text{AREA RMST}=(10-\int_0^{10}F(t)dt/10)*100$$

237

238 Pooled HRs and Kaplan-Meier were calculated and created using Stata19 (StataCorp. 2025. Stata
239 Statistical Software: Release 19. College Station, TX: StataCorp LLC) and R: A Language and
240 Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria,
241 2024; <https://www.R-project.org>). Estimates of random and fixed effects were presented by means
242 of forest plots.

244 ***Ethics Statement***

245 This meta-analysis used data extracted from previously published population-based cohort studies.
246 All included studies had obtained the necessary ethical approvals from their respective institutional
247 review boards, as documented in the original publications.

248

249

250 **RESULTS**

251 *Quality Assessment of Meta-analyses*

252 *Risk of Bias*

253 The methodological quality of the evidence was rigorously evaluated using the Modified
254 Newcastle-Ottawa Scale (NOS), which revealed a generally high standard across the included
255 literature. Specifically, 93.75% of the studies were determined to be high-quality, achieving ratings
256 between 7-9 stars. Within this distribution, four studies received the maximum of 9 stars, while
257 eleven received 7 or 8 stars, reflecting robust study designs. Only a single study was rated with 6
258 stars. Regarding the inclusion of randomised controlled trials (RCTs), one study raised concerns
259 about the risk of bias judgment, specifically characterised by an unpredictable direction of bias, as
260 detailed in the Supplementary Material Tables 3 and 4.

261

262

263 **RMCI and RMST Analysis: The Clinical Burden of MACE**

264 To translate dosimetric risk into a tangible clinical impact, we conducted a comprehensive
265 assessment of the disease burden over a 10-year horizon using Restricted Mean Cumulative
266 Incidence models. Based on available Kaplan-Meier curves, the estimated cumulative incidence of
267 MACE was 11.4% at 5 years, rising significantly to 23.9% at 10 years after completion of
268 radiotherapy. The total burden of disease, quantified as the area subtended by the cumulative
269 incidence curves, yielded an overall mean value of 116.8%*years across the cohorts. However, the
270 analysis revealed striking disparities when stratified by individual baseline risk profiles: while the
271 burden remained relatively low in the cohorts of Chang and the no-plaque subgroup of Van den
272 Bogaard (both at 46.4%*years), it escalated dramatically to 166.6%*years in the study by Lai and
273 reached a peak of 208.8%*years in patients with pre-existing atheromatous plaques. These findings
274 provide a clear, quantifiable metric of the time at risk, highlighting how the presence of coronary
275 calcification acts as a potent multiplier of the long-term clinical burden (Figure 2).

276 **Quantification of the 10-Year Clinical Burden: Years of Health Lost**

277 The Restricted Mean Cumulative Incidence - Burden (RMCI-B) analysis was employed to quantify
278 the average number of health years lost specifically due to MACE within the ten-year observation

279 window. While the overall mean across all cohorts was estimated at 0.991 years, stratification of the
280 data revealed substantial clinical disparities by individual risk profile. Patients in the Chang cohort
281 (0.347 years) and the Van den Bogaard subgroup without pre-existing plaques (0.386 years)
282 demonstrated a relatively contained loss of health. Conversely, the burden increased drastically in
283 the Lai cohort (1.522 years) and reached its peak in patients with documented atheromatous
284 plaques, who lost an average of 1.711 years of health.

285 These findings demonstrate that, within the same timeframe, a patient with a high baseline risk
286 profile may lose nearly 5 times as many health years as a low-risk counterpart. This significant gap
287 underscores that the clinical impact of radiotherapy is not uniform, underscoring the need for
288 predictive models that integrate both dosimetric parameters and individual biological characteristics
289 to accurately estimate the long-term cardiac toll.

290 **Total Disease Burden: Cumulative Impact over 10 Years**

291 To further elucidate the long-term impact of radiotherapy, the Total Burden was calculated by
292 integrating the area under the cumulative incidence curves for each cohort. The overall mean total
293 burden across the analysed studies was 1.168 years. Similar to the average health loss, the total
294 burden exhibited a strong correlation with baseline cardiovascular risk factors. In lower-risk
295 cohorts, such as Chang and the no-plaque subgroup of Van den Bogaard (2021), the total years lost
296 remained consistent at 0.464. However, this value escalated to 1.666 years in the Lai cohort and
297 peaked at 2.088 years in patients with pre-existing atheromatous plaques. These cumulative metrics
298 show that, for high-risk individuals, more than 20% of the 10-year observation period is spent on
299 clinical management or the consequences of MACE (Figure 2).

300 **MACE-Free Survival: Restricted Mean Survival Time (RMST) Analysis**

301 A Restricted Mean Survival Time (RMST) analysis was performed to calculate the average duration
302 patients remained entirely free from MACE within the 10-year post-radiotherapy window. The
303 overall mean MACE-free survival across all cohorts was 8.832 years.

304 Consistent with the RMCI findings, the RMST results showed a significant divergence across
305 patients' basal risk profiles. In the low-risk cohorts, represented by Chang and the no-plaque
306 subgroup of Van den Bogaard, patients enjoyed a MACE-free period of 9.536 years. In contrast, this
307 period was notably reduced in the Lai cohort (8.334 years) and reached its minimum in patients
308 with pre-existing atheromatous plaques, who remained free from events for only 7.912 years.

309 By quantifying the area under the RMST Kaplan-Meier curves, we further determined the
310 percentage of disease-free time over the decade. The overall mean was 88.32%, ranging from

311 95.36% in low-risk individuals to 79.12% in high-risk patients. These metrics provide a definitive
312 measure of the therapeutic window of cardiovascular safety, showing that baseline coronary disease
313 shortens the disease-free interval by more than 1.6 years compared with healthy counterparts
314 (Figure 3).

315 **Disease-Free Time Proportion: Area under the RMST Curve**

316 The clinical impact of these findings is further elucidated by estimating the area subtended by the
317 RMST Kaplan-Meier curves, which provides the percentage of disease-free time within the 10-year
318 observation period. The overall mean across the studies was 88.32%, indicating that, on average,
319 more than 11% of the first decade post-radiotherapy is affected by the clinical burden of MACE.

320 However, the disparity between risk profiles remains the most significant finding. Both the Chang
321 cohort and the no-plaque subgroup of Van den Bogaard confirmed a high disease-free proportion of
322 95.36%. In contrast, this percentage dropped to 83.34% in the Lai cohort and reached its lowest
323 point in the Van den Bogaard with-plaque subgroup, at 79.12%. These percentages translate the
324 abstract concept of risk into a concrete measure of patient well-being: high-risk individuals spend
325 approximately 20% of their 10-year follow-up period managing or suffering from major coronary
326 complications. This definitive metric reinforces the study's call for a paradigm shift toward
327 personalised, risk-stratified cardiovascular monitoring in breast cancer survivors (Figure 6).

328

329

330

331 **Figure 2. Cumulative Incidence of Major Acute Cardiac Events**

332 Extrapolated Kaplan-Meier curves with pooled mean. The x-axis value represents the period on
333 time in years while the y-axis estimates the cumulative incidence in percentage.

334

335 **Figure 3. Probability MACE-free period curve**

336 Extrapolated Kaplan-Meier curves with pooled mean. The x-axis represents the period on time in
337 years while the y-axis estimates the probability of MACE-free in percentage.

338

339 ***Incidence of acute coronary events - Mean Heart Dose***

340 The relationship between the incidence of acute coronary events and Mean Heart Dose (MHD) was analysed
 341 using data from Van den Bogaard (2021) and Zureick et al., with an average patient follow-up of 6.5 years.
 342 Notably, the analysis for Van den Bogaard accounted for two distinct variables: MHD exposure in patients
 343 with and without pre-existing coronary atheromatous plaques.
 344 Data were pooled using both fixed and random-effects models. Significant statistical heterogeneity was
 345 observed ($\tau^2=1.95$; $I^2=99.11\%$; $H^2=112.45$), although the test for subgroup differences remained non-
 346 significant ($Q(2)=1.81$, $p=0.404$). The pooled estimate demonstrated a significant increase in the overall
 347 Hazard Ratio for cardiotoxicity following radiotherapy, with a value of 1.17 (95% CI: 1.02-1.34). The
 348 prediction interval, also ranging from 1.02 to 1.34, further supports the consistency of this increased risk
 349 across the included studies (Figure 4).
 350 To validate the robustness of these meta-analytic findings, sensitivity analyses-including a leave-one-out
 351 assessment-were performed by sequentially excluding each study. Publication bias was evaluated through a
 352 funnel plot and Egger's test. While Egger's test indicated a potential small-study effect ($p=0.0015$), a
 353 subsequent trim-and-fill analysis yielded an adjusted estimate of 1.031 (95% CI: 1.004-1.060) without the
 354 need to impute additional studies. This narrow confidence interval, consistently remaining above unity,
 355 suggests that the overall effect is robust and that publication bias does not significantly compromise the
 356 results.
 357 Furthermore, study-specific effects, precision, and heterogeneity were visualised using Galbraith, profile
 358 likelihood, and Baujat plots. These detailed diagnostic assessments confirm the stability of the pooled
 359 estimate despite the observed variance (see Supplementary Table 6 and Figures 1-7).
 360
 361 **Figure 4.** HR with 95% C.I. for cardiotoxicity radiotherapy induced in breast cancer related to
 362 mean heart dose. Individual and combined hazard ratio (with 95% confidence intervals and 89%
 363 confidence intervals). Fixed and REML- effect statistical model were performed. The size of the
 364 boxes is proportional to the weight ($1/SE$) of each study. Prediction interval is visibly reported as a
 365 rectangle. Van den Bogaard et al. has two different variables: MHD on coronary arteries,
 366 respectively with and without atheromatous plaque in the LAD, reported in the plot.

367

368

369 ***Incidence of acute coronary events - Left Anterior Descending Artery Mean Dose***

370

371 The analysis of the mean dose to the Left Anterior Descending LAD artery involved pooling data
 372 through both fixed-effects and random-effects REML models. The heterogeneity assessment
 373 revealed substantial variance among the studies ($\tau^2=0.51$; $I^2=85.30$; $H^2=6.80$), with the test

374 for subgroup differences approaching, but not reaching, the standard threshold for significance
375 ($Q(2)=10.22$, $p<0.06$).

376 The fixed-effect model indicated a statistically significant pooled effect of 1.03 (95% CI: 1.00-
377 1.06). However, when applying the REML model, which more conservatively accounts for the
378 observed heterogeneity, the overall Hazard Ratio for cardiotoxicity following radiotherapy was 1.10
379 (95% CI: 0.98-1.23). The corresponding prediction interval was estimated at 0.89-1.36 (Figure 5).
380 Regarding publication bias, Egger's test yielded a non-significant result ($p=0.2090$). Furthermore,
381 the trim-and-fill analysis yielded an estimate of 1.168 (95% CI: 1.021-1.338), suggesting that
382 publication bias does not compromise the integrity of the primary analysis

383 To further investigate study-specific effects and precision, as well as to evaluate the sources of
384 heterogeneity, Galbraith, Profile Likelihood, and Baujat plots were generated (Supplementary Table
385 7 and Figures 8-14). The robustness of these meta-analytic findings was confirmed through
386 sensitivity and leave-one-out analyses, in which individual studies were sequentially excluded to
387 assess the stability of the pooled estimates.

388
389 **Figure 5.** HR with 95% C.I. for cardiotoxicity radiotherapy induced in breast cancer related to LAD
390 mean dose. Individual and combined hazard ratio (with 95% confidence intervals and 89%
391 confidence intervals). Fixed and REML- effect statistical model were performed. The size of the
392 boxes is proportional to the weight ($1/SE$) of each study. Prediction interval is visibly reported as a
393 rectangle. Van den Bogaard et al. has two different variables: MHD on coronary respectively with
394 and without atheromatous plaque, reported in the plot.

395
396
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399

400 ***Cumulative Incidence of Acute Coronary Events***

401 The cumulative incidence of acute coronary events was estimated from data by Cao et al. (2024)
402 and Van den Bogaard et al. (2017), with a mean patient follow-up of 4.8 years. Data were
403 synthesised using both fixed and random-effects models. The heterogeneity analysis showed an I^2
404 of 98.82% ($\tau^2=23.40$; $H^2=1.00$), although the test for subgroup differences remained non-
405 significant ($Q(2)=0.54$, $p=0.464$).

406 The pooled analysis demonstrated an increased overall HR for cardiotoxicity following
407 radiotherapy of 1.15 (95% CI: 1.00-1.32), with a corresponding prediction interval of 1.00-1.32
408 (Figure 6). This suggests a consistent trend toward increased cardiovascular risk, even within the
409 relatively short follow-up period of these cohorts.

410 Regarding publication bias, Egger's test yielded $p=1.00$; however, the standard error indicated poor
411 model fit, prompting a trim-and-fill analysis. The results of this analysis (1.149; 95% CI: 0.997-
412 1.324) indicated that no studies were missing (0 imputed), suggesting that the effect size estimation
413 is robust and that this method remains unadjusted for potential publication bias. To further explore
414 study-specific effects and the sources of variance, Galbraith, Profile Likelihood, and Baujat plots
415 were utilised (Supplementary Table 8 and Figures 15-21). Additionally, sensitivity and leave-one-
416 out analyses were conducted by sequentially excluding each study, confirming the stability and
417 strength of the meta-analytic findings as detailed in the supplementary materials.

418 **Figure 6.** HR with 95% C.I. for cardiotoxicity radiotherapy induced in breast cancer related to
419 cumulative incidence. Individual and combined hazard ratio (with 95% confidence intervals and
420 89% confidence intervals). Fixed and REML- effect statistical model were performed. The size of
421 the boxes is proportional to the weight ($1/SE$) of each study. Prediction interval is visibly reported
422 as a rectangle.

423
424
425

426 ***Certainty of Evidences***

427 Despite the high NOS scores, the GRADE assessment highlighted a more nuanced landscape, with
428 the certainty of evidence ranging from very low to moderate. Moderate-certainty evidence was
429 identified in only 23.53% of the studies, which were typically characterised by large-scale, well-
430 designed observational cohorts utilising individual dosimetry and strict MACE endpoints.
431 Conversely, approximately 60% of the studies fell into the low or very low certainty categories due
432 to significant methodological and applicability limitations.

433 The most frequent domains leading to GRADE downgrading across the evidence base were
434 indirectness and imprecision. Indirectness was rated as serious or very serious in 80% of the studies,
435 largely because researchers often relied on surrogate outcomes, such as GLS decline, strain
436 abnormalities, or troponin rise, rather than hard clinical MACE. Furthermore, imprecision was a
437 serious concern in nearly 70% of the analyses. This confirms the earlier methodological premise
438 that many studies remain underpowered to perform effective subgroup analyses or to establish

439 reliable dose-response modelling, particularly at low-dose thresholds. Finally, selection bias related
440 to imaging-based cohorts and limited blinding of outcome assessments further contributed to the
441 overall downgrading of evidence certainty. (Supplementary Table 5)

442

443 ***Discussion***

444 To the best of our knowledge, this is the first meta-analysis of cardiotoxicity related to radiation risk
445 in BC. This meta-analysis and clinical burden assessment represent the first significant evolution in
446 our understanding of radiotherapy-induced cardiotoxicity. While historical data, most notably the
447 landmark study by Darby et al., established a linear relationship between mean heart dose and major
448 coronary events, our findings refine this paradigm. By shifting the focus toward cardiac
449 subvolumes, specifically the Left Anterior Descending artery, and introducing the Restricted Mean
450 Cumulative Incidence, we provide a novel framework for quantifying the actual time-loss of health
451 in breast cancer survivors.

452 ***The Temporal Shift: Cardiotoxicity as an Early Clinical Burden***

453 A compelling finding of our RMCI analysis is the early manifestation of significant cardiac burden.
454 While historical literature emphasised a clinical latency of 15 to 20 years or more, our data
455 demonstrate substantial health loss much earlier. At just 10 years post-radiotherapy, the average loss
456 of health is already 0.991 years (nearly a full year). This suggests that modern cardiotoxicity,
457 perhaps due to the interaction with increasing baseline metabolic risks in the current population,
458 manifests significantly sooner than previously estimated. Waiting until the 15-year mark to initiate
459 intensive follow-up may miss a critical window for early intervention.

460 ***The Predictive Paradox: Mean Heart Dose vs LAD Granularity***

461 A critical comparison in our study is the performance of Mean Heart Dose versus LAD dosimetry.
462 Statistically, the MHD showed a higher pooled Hazard Ratio (1.17) compared to the LAD (HR
463 1.10). Notably, the LAD estimate in the REML model did not reach statistical significance at the
464 95% level (95%CI: 0.98-1.23).

465 However, this predictive paradox must be interpreted through the lens of methodological precision.
466 The high heterogeneity for the LAD ($I^2 = 85\%$) reflects the inherent difficulties in cardiac
467 subvolume dosimetry. Unlike the whole heart, the LAD is a small, mobile structure; contouring
468 errors and cardiac motion during CT simulation introduce a noise that can dilute the statistical
469 strength of the LAD as a predictor. While the MHD appears more stable in meta-analytical models,

470 the high heterogeneity of the LAD suggests that its true impact might be underestimated due to
471 current technical limitations in vessel segmentation.

472 ***The Multiplier Effect: From Dose-Dependent to Patient-Specific Risk***

473 The introduction of the RMCI-Burden metric allows us to move beyond a purely dose-dependent
474 model toward a patient-specific paradigm. Our findings demonstrate that the biological terrain is
475 just as critical as the radiation dose. The presence of pre-existing atheromatous plaques acts as a
476 clinical multiplier: patients with plaques lose 1.711 years of health, whereas those without plaques
477 lose only 0.386 years.

478 This fourfold increase in health loss indicates that radiotherapy does not merely cause damage; it
479 accelerates pre-existing vascular frailty. This is a crucial distinction for modern oncology: a safe
480 dose for a healthy 40-year-old may be profoundly toxic for a 60-year-old with subclinical
481 atherosclerosis. While the dose counts, the presence of a plaque multiplies the damage by four,
482 necessitating much more stringent dose constraints and aggressive cardio-protection for this specific
483 subgroup.

484

485 ***Strengths and Limitations***

486 This meta-analysis has several strengths that enhance the clinical applicability of its findings. The
487 formal quality appraisal used validated instruments, thereby limiting selection and information
488 bias. The inclusion of contemporary cohorts with detailed dosimetry for both mean heart dose and
489 coronary substructures, combined with advanced time-to-event modelling based on RMCI and
490 RMST derived from Kaplan-Meier curves, allows a granular and intuitively interpretable
491 characterisation of the 10-year cardiac burden after breast radiotherapy. Furthermore, the use of
492 complementary fixed-effect and random-effects models, together with extensive sensitivity,
493 heterogeneity, influence and small-study effect analyses, suggests that the principal conclusions are
494 robust across a wide range of analytical assumptions.

495 Despite the robust statistical framework provided by the RMCI and RMST analyses, several
496 confounding factors must be addressed. A significant limitation is the lack of granular data
497 regarding systemic therapy. While the use of anthracyclines, taxanes, and trastuzumab is
498 documented, there is no clear distinction between cohorts receiving chemotherapy versus those
499 managed with radiotherapy alone. Given the well-established synergistic cardiotoxicity between
500 these treatments, the inability to isolate these effects remains a source of potential bias.

501 Furthermore, heterogeneity is introduced by the evolution of radiotherapy techniques, surgical
502 approaches (mastectomy vs breast-conserving surgery), and different tumour stages (e.g., higher N+
503 stages requiring more extensive nodal irradiation). Our dataset spans, in the systematic review
504 segment, from older high-dose techniques to modern, low-dose IMRT/VMAT procedures combined
505 with Deep Inspiration Breath Hold (DIBH).

506 Lastly, the GRADE assessment indicates a very low certainty of results, a common finding in
507 epidemiological meta-analyses, where multiple confounding variables, from socio-economic
508 disparities across countries to varying covariate adjustments, preclude a higher rating. However, by
509 capturing the entire trajectory of the cumulative incidence curve, an endpoint increasingly endorsed
510 by the FDA and EMA, this study provides the most comprehensive and clinically intuitive estimate
511 of the long-term cardiac toll currently available.

512 In conclusion, this study demonstrates that radiation-induced heart damage is a substantial clinical
513 burden that manifests within the first decade of treatment. By translating statistical risk into a
514 concrete temporal dimension, we revealed that the presence of baseline atheromatous plaques
515 quadruples the loss of healthy years. Our results strongly advocate for baseline cardiovascular
516 screening, such as Calcium Scoring, to identify high-risk patients. For these individuals, the
517 adoption of advanced techniques like DIBH and restricted dose constraints is no longer a technical
518 option but a clinical necessity to preserve years of disease-free life.

519

520 ***Critical View***

521 This review provides the first meta-analysis specifically quantifying radiation-induced
522 cardiotoxicity in breast cancer patients treated with postoperative radiotherapy. By combining
523 traditional dose-response modelling with Restricted Mean Cumulative Incidence and Restricted
524 Mean Survival Time, we translate cardiac exposure into years of MACE-free life lost within 10
525 years, offering to oncologist and physicians an intuitive complement to prior work focused mainly
526 on mortality. Our findings highlight that pre-existing coronary plaques markedly amplify the
527 clinical burden, underscoring the need for risk-adapted dose constraints and cardioprotective
528 strategies. The scope of this meta-analysis is limited to studies reporting clinical MACE endpoints
529 with adequate heart or LAD dosimetry and a 10-year horizon with strict criteria; we do not
530 systematically cover non-cardiac toxicities.

531

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702

703 **CRedit Authorship Contributions**

704 Enrico Altiero Giusto, MD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead;
705 Investigation: Lead; Methodology: Lead; Software: Equal; Validation: Equal; Visualization: Equal;
706 Writing – original draft: Lead; Writing – review & editing: Equal).

707 Caterina Boncompagni, PhD (Conceptualization: Equal; Investigation: Supporting; Methodology:
708 Equal; Validation: Equal; Writing – review & editing: Equal).

709 Delia Anamaria Bogdan, MSc (Conceptualization: Equal; Investigation: Supporting; Methodology:
710 Equal; Validation: Equal; Writing – review & editing: Equal).

711 Vittorio Oteri, MD (Conceptualization: Equal; Investigation: Supporting; Methodology: Equal;
712 Validation: Equal; Writing – review & editing: Equal).

713 Milena Gabbani, MD (Conceptualization: Equal; Investigation: Supporting; Methodology: Equal;
714 Validation: Equal; Writing – review & editing: Equal).

715 Paolo Pinton, PhD, Prof (Conceptualization: Equal; Investigation: Supporting; Methodology: Equal;
716 Validation: Equal; Writing – review & editing: Equal).

717 Carlotta Giorgi, PhD, Prof (Conceptualization: Equal; Investigation: Equal; Methodology: Equal;
718 Validation: Equal; Writing – review & editing: Equal).

719 Francesco Fiorica MD, PhD, Prof (Conceptualization: Equal; Investigation: Equal; Data curation:
720 Supporting; Methodology: Equal; Validation: Equal; Visualization: Equal; Writing – original draft:
721 equal; Writing – review & editing: Equal).

722

723 ***Ethics Statement***

724 This meta-analysis used data extracted from previously published population-based cohort studies.
725 All included studies had obtained the necessary ethical approvals from their respective institutional
726 review boards, as documented in the original publications.

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Data Transparency Statement:

The data, analytic methods, and study materials used in this research will be made available to other researchers upon adequate request.

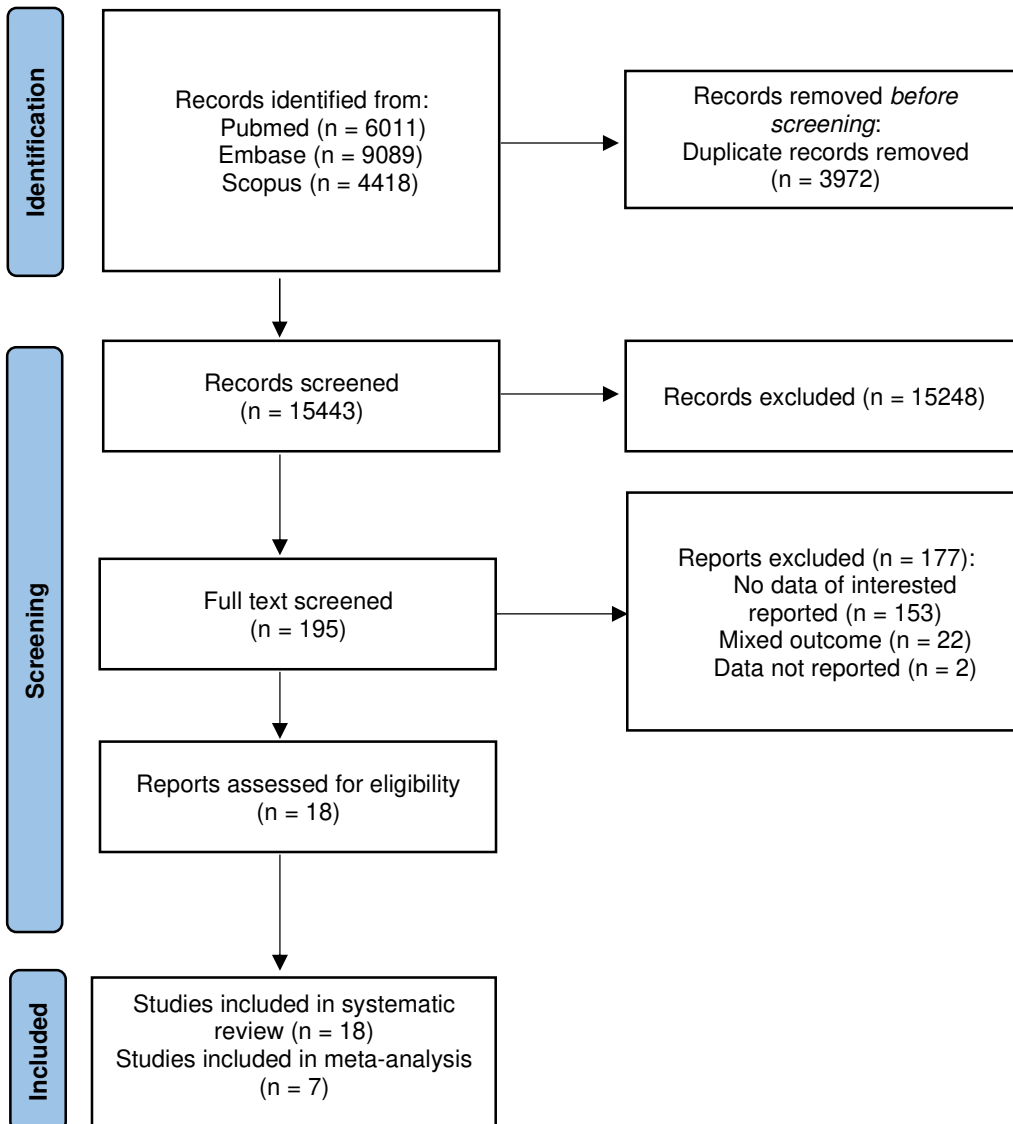
Conflicts of interest

The authors disclaim no conflicts of interest.

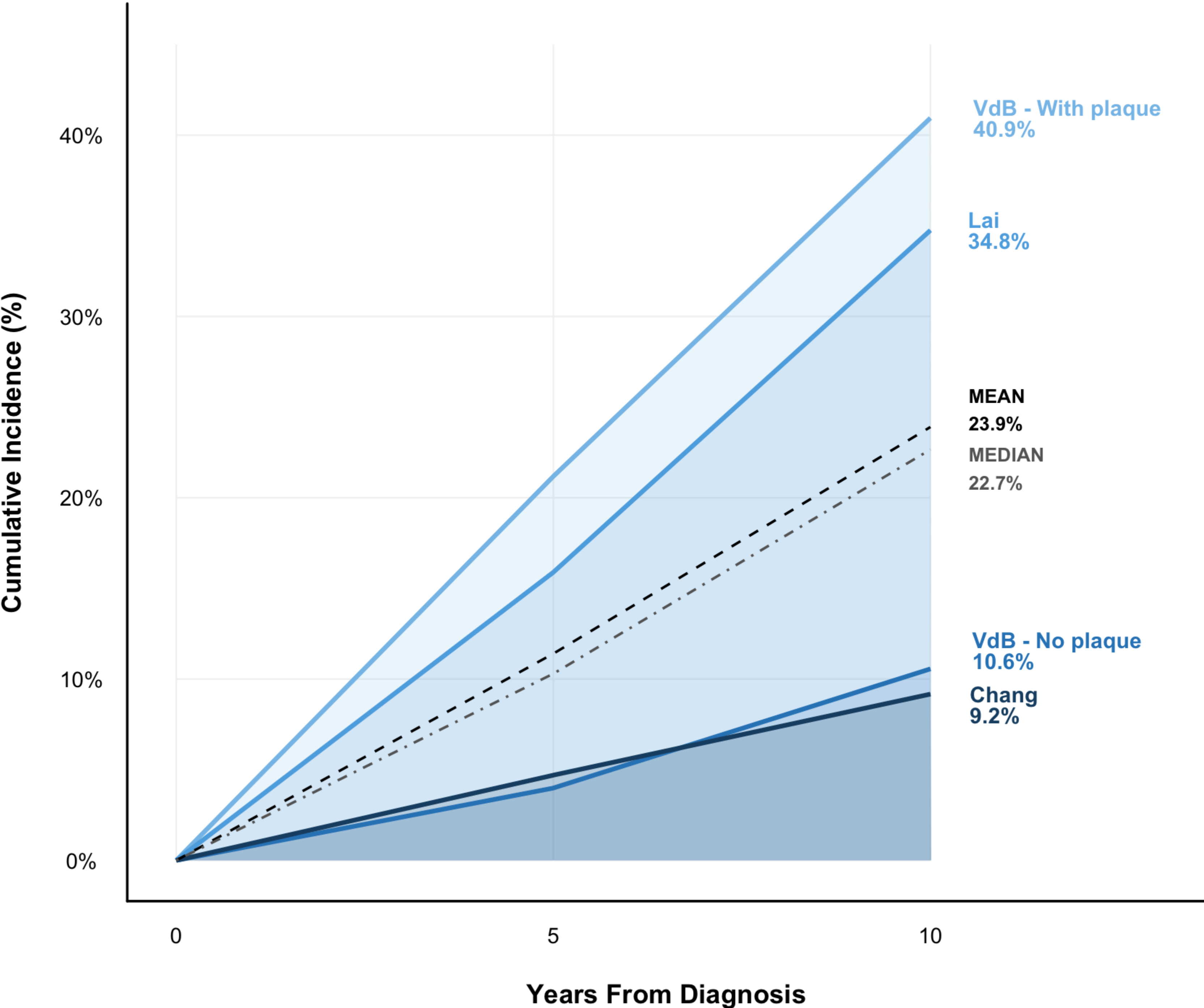
Founding Source

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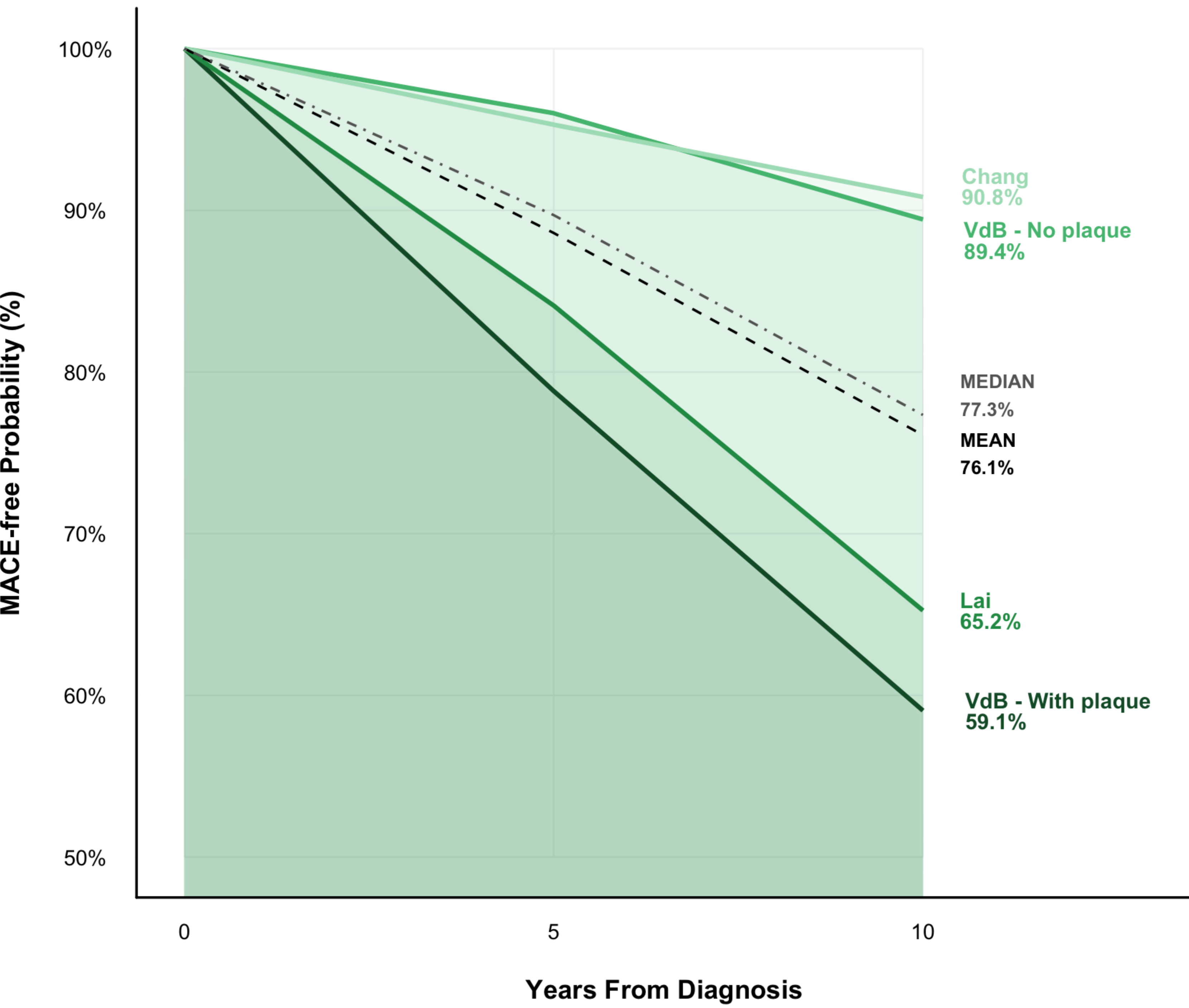
Identification of studies via databases and registers

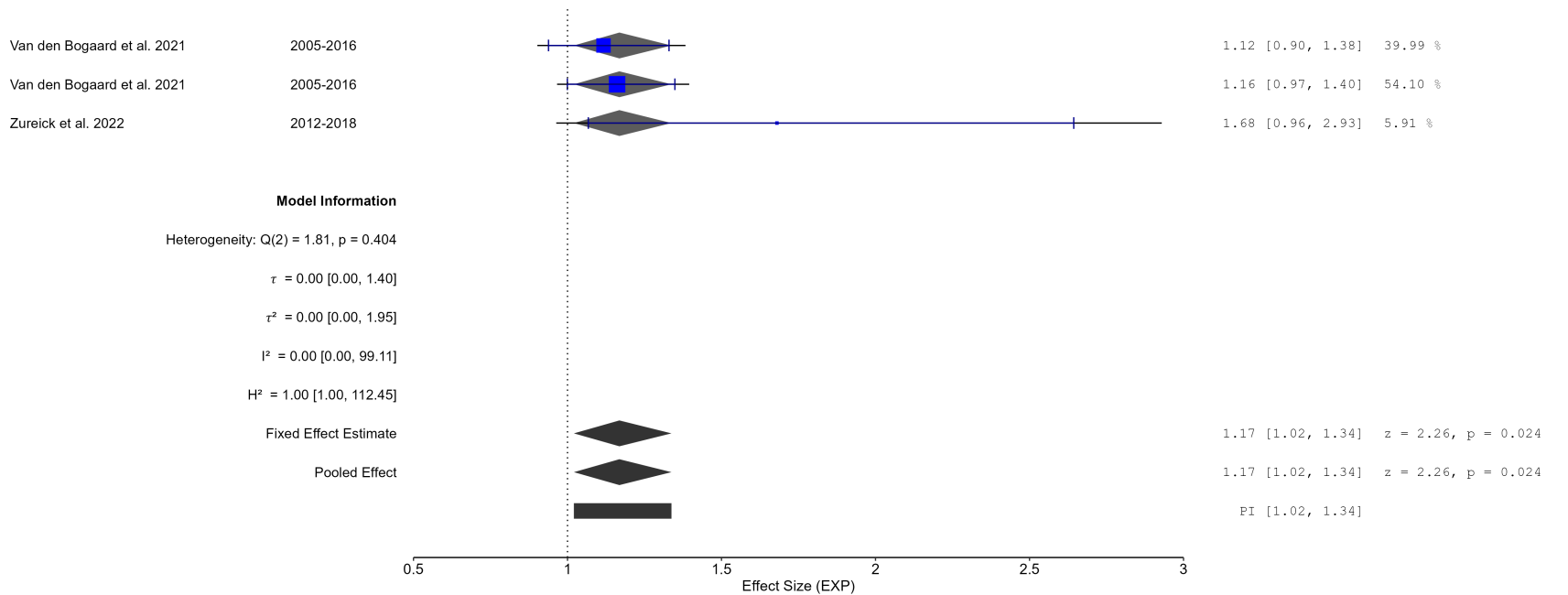


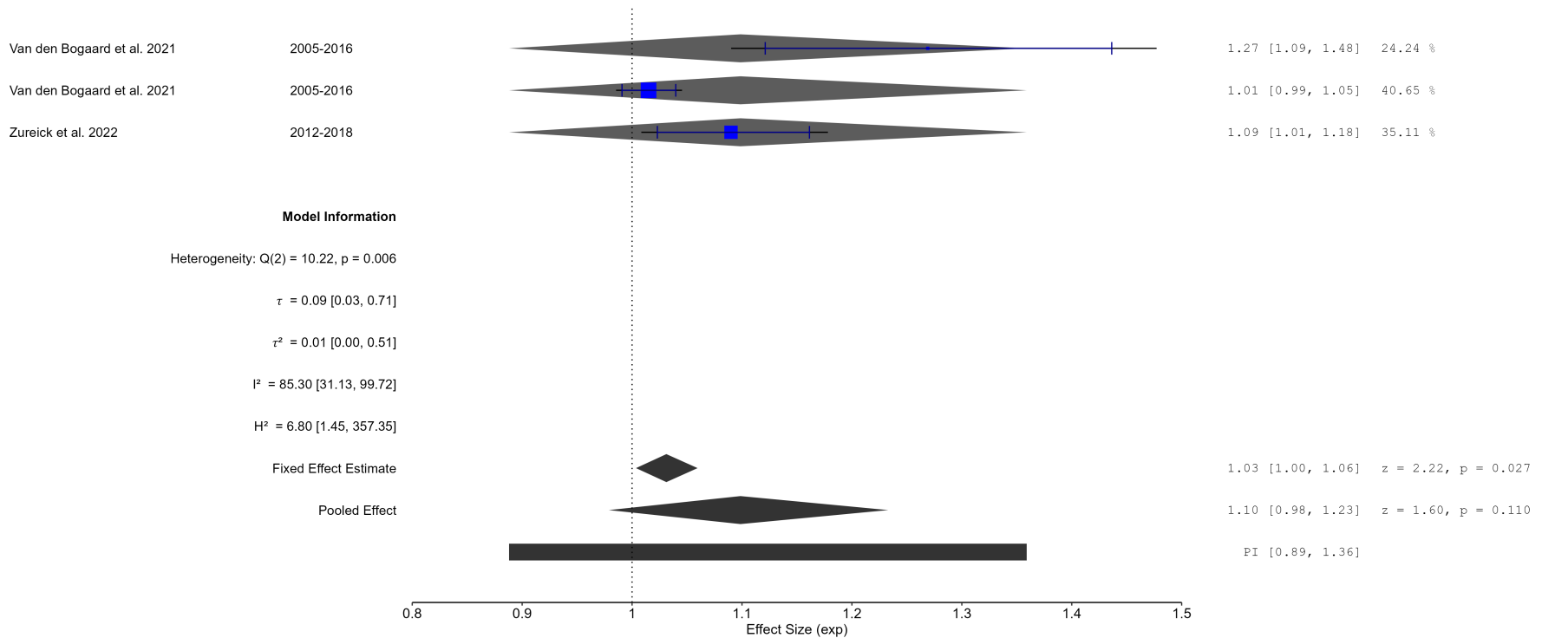
Cumulative Incidence of MACE

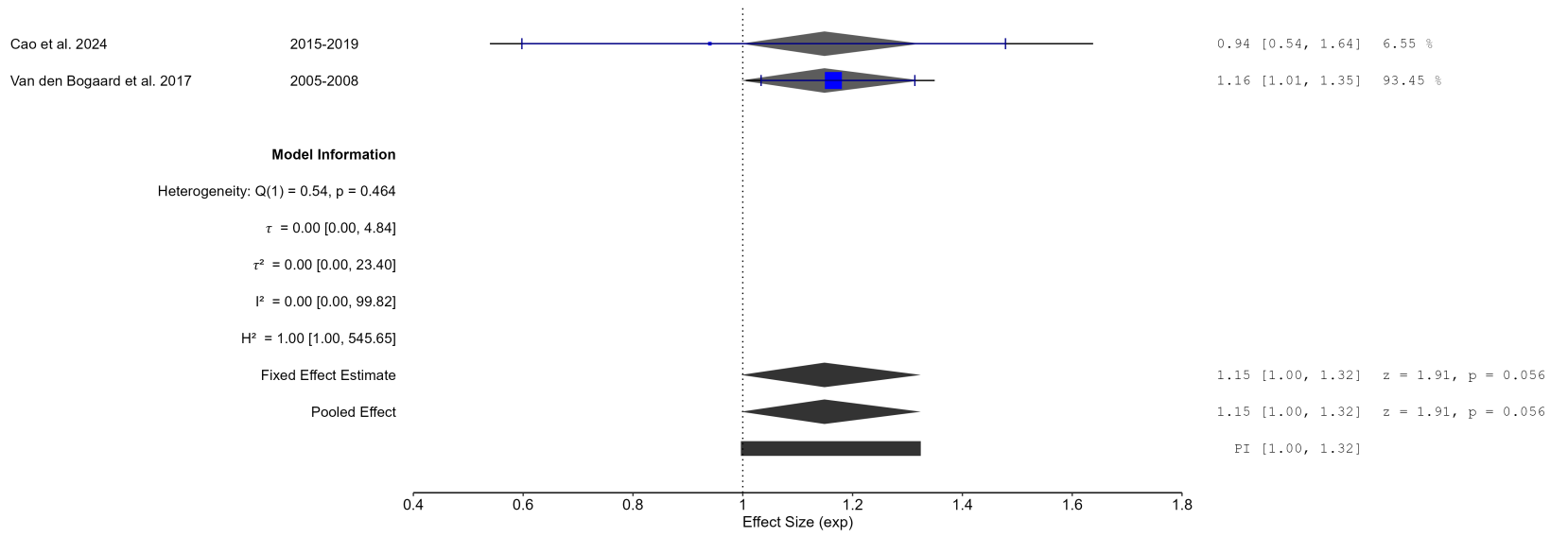


Probability of MACE-free Survival









Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.GUIDELINETABLE.docx](#)
- [SupplementaryMaterialsRTpBC.docx](#)