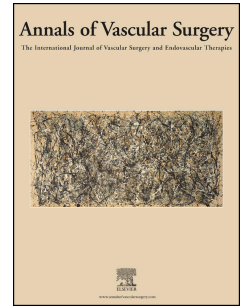# Journal Pre-proof

Population-based Assessment of Aortic-related Outcomes in Aortic Dissection, Intramural Hematoma, and Penetrating Aortic Ulcer

Salome Weiss, Indrani Sen, Ying Huang, W. Scott Harmsen, Thomas C. Bower, Gustavo S. Oderich, Philip P. Goodney, Randall R. DeMartino

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1   **Population-based Assessment of Aortic-related Outcomes in Aortic Dissection, Intramural**

2   **Hematoma, and Penetrating Aortic Ulcer**

3

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Abstract

Objective: Aim was to analyze aortic-related outcomes after diagnosis of aortic dissection (AD),

intramural hematoma (IMH), and penetrating aortic ulcer (PAU) from a population-based

approach.

Methods: Retrospective review of an incident cohort of AD, IMH, and PAU patients in Olmsted

County, MN from 1995-2015. Primary end-point was aortic death. Secondary end-points were

subsequent aortic events (aortic intervention, new dissection or rupture not present at

presentation) and first-time diagnosis of an aortic aneurysm. Outcomes were compared to

randomly selected population referents matched for age and sex in a 3:1 ratio using Cox

proportional hazards regression adjusting for comorbidities.

Results: Among 133 patients (77 AD, 21 IMH, 35 PAU), 57% were male and mean age was 71.8

years (SD 14). Median follow-up was 10 years. Of 73 deaths among AD/IMH/PAU patients, 23

(32%) were aortic-related. Estimated freedom from aortic death was 84%, 80% and 77% at 5, 10,

and 15 years. There were no aortic deaths among population referents (adjusted HR for aortic

death in AD/IMH/PAU 184.7, 95% CI 10.3 – 3299.2, p<.001). Fifty (38%) AD/IMH/PAU

patients had a subsequent aortic event (aortic intervention, new dissection or rupture) while there

were eight (2%) aortic events among population referents (all elective aneurysm repairs; adjusted

HR for any aortic event and aortic intervention in AD/IMH/PAU patients 33.3, 95% CI 15.3 –

72.0, p<.001 and 31.5, 95% CI 14.5 – 68.4, p<.001, respectively). After excluding aortic

events/interventions ≤14 days of diagnosis, AD/IMH/PAU patients remained at increased risk of

any aortic event (adjusted HR 10.8, 95% CI 3.9 – 29.8, p<.001) and aortic intervention (adjusted

HR 9.6, 95% CI 3.4 – 26.8, p<.001). Among those subjects with available follow-up imaging, the

risk of first-time diagnosis of aortic aneurysm was significantly increased for AD/IMH/PAU

47 patients when compared to population referents (adjusted HR 10.9, 95% CI 5.4 – 21.7, p<.001

48 and 8.3, 95% CI 4.1 – 16.7, p<.001 for thoracic and abdominal aneurysms respectively) and

49 remained increased when excluding aneurysms that formed within 14 days of AD/IMH/PAU

50 (adjusted HR of 6.2, 95% CI 1.8 – 21.1, p=.004 and 2.8, 95% CI 1.0 – 7.6, p=.040 for thoracic

51 and abdominal aneurysms respectively).

52 **Conclusions:** AD/IMH/PAU patients have a substantial risk of aortic death, any aortic event,

53 aortic intervention, and first-time diagnosis of aortic aneurysm that persists even when the acute

54 phase (≤14 days after diagnosis) is uncomplicated. Advances in post-diagnosis treatment are

55 necessary to improve the prognosis in these patients.

56

57 **Key words:** Aortic dissection, intramural hematoma, penetrating aortic ulcer, aneurysm,

58 prognosis.

59

66

67 **Disclosures:** None.

1. Introduction

Aortic dissection (AD), intramural hematoma (IMH) and penetrating aortic ulcer (PAU) are dreaded aortic pathologies. Despite the distinct characteristics of each of these entities, they all involve a disruption of the media layer of the aortic wall and may progress from one to another,[1] sharing a significant risk of acute and chronic aortic-related morbidity and mortality.[2] For acute Stanford type A and type B dissection, the International Registry of Acute Aortic Dissection (IRAD) reported an in-hospital mortality of 22% and 14% respectively.[3] At three years, almost 25% of those with type B dissection discharged alive will additionally have died.[4] In both, type A and type B dissection, aortic events are the most common cause of death.[5-8] Acute survival of patients presenting with IMH and PAU may be slightly better than for those with AD (9-13%)[9, 10] but poor long-term survival has been reported in an institutional series.[10] Additionally, patients with chronic AD, IMH, and PAU carry a significant risk of subsequent aortic events including recurrent dissection, rupture, and aneurysmal degeneration, often requiring intervention. However, the true risk of late aortic death and subsequent aortic events among patients with these aortic pathologies is not well known. Most long-term data come from registries or single centers[4, 10-12] and may be biased by limited follow-up compliance of these patients[13] and lack of mortality data.

We have previously characterized the incidence of AD, IMH, and PAU and its associated mortality in a population-based approach using the Rochester Epidemiology Project (REP, Olmsted County, MN residents)[14] and evaluated this incidence cohort in regards to non-aortic cardiovascular events.[15] The objective of the present study was to quantify the risk of aortic death, subsequent aortic events, and aortic aneurysm formation after AD, IMH, and PAU. By comparing AD, IMH, and PAU patients to referent subjects from the same population, we aimed

91   to approximate the expected increased risk of AD, IMH, and PAU patients in order to

92   characterize the early and late impact of these aortic pathologies on patients' lives.

93

94   **2. Methods**

95   The detailed identification process of the incidence cohort we assessed is described elsewhere.[14,

96   15] In brief, we utilized the resources of the REP, a unique collaboration of health care providers

97   linking together medical records of virtually all residents of Olmsted County, MN.[16, 17] This

98   permits the identification of incident diagnoses at a population level and allows follow-up of

99   patients across providers. Within the REP, adult residents (≥18 years of age) with a new

100 diagnosis of AD, IMH, or PAU from 1995-2015 were identified using International Classification

101 of Disease codes (ICD, 9th and 10th revision) and Hospital Adaptation of the International

102 Classification of Diseases codes (HICDA, 2nd edition). Study inclusion required imaging

103 confirmation of the diagnosis. For immediate decedents, AD/IMH/PAU had to be confirmed by

104 autopsy or be the primary diagnosis on the death certificate. AD, IMH, and PAU were defined

105 based on standard criteria used in current guidelines[1] and classified as acute (≤14 days of

106 symptom onset), subacute (15 – 90 days), chronic (>90 days), or unknown presentation

107 (unknown date of onset of the pathology). AD was classified using the De Bakey and the

108 Stanford classification, while IMH was classified using the Stanford classification only. PAU was

109 classified by anatomic location.

110 The AD/IMH/PAU cohort was compared to randomly selected Olmsted County population

111 referents matched for age and sex. As previously described, a matching ratio of 3:1 was chosen

112 based on a sample size calculation to detect a minimum hazard ratio (HR) for all-cause death of

113 1.95 with an alpha of 0.05 and power of 0.8.[14] For population referents, the diagnosis date of the

114 matched AD/IMH/PAU patient was set as the index date to differentiate pre-existing conditions

115 from outcome events. Comorbidities were assessed using the Charlson Comorbidity Index.[18]

116 Charlson comorbidities were identified using predefined ICD and HICDA codes. Assignment of

117 a comorbidity required two occurrences of a corresponding code within five years prior to the

118 date of AD/IMH/PAU diagnosis (or the index date in population referents).[19] All individuals

119 were censored on December 31, 2015 for outcomes.

120

121 *2.1. Assessment of aortic death*

122 Primary endpoint was aortic death. Dates and causes of death were obtained from death

123 certificates available through the REP, which collates up to date information on in state and out

124 of state deaths from multiple sources.[17] For a minority of subjects with missing vital status

125 information (e.g. due to migration), an institutionally approved Internet research location service

126 (Accurint, www.accurint.com) was used and death certificates requested where permissible as per

127 state laws. For three AD/IMH/PAU patients and three population referents known to have died

128 out of state, deaths certificates could not be obtained. Causes of death retrieved from death

129 certificates were cross-checked with medical records. Aortic death was defined as death due to

130 rupture, ischemic complications, surgical complications related to AD/IMH/PAU treatment, and

131 other aortic-related causes (not specified).

132

133 *2.2. Assessment of subsequent aortic events*

134 The secondary end-point of a subsequent aortic event included aortic intervention, and new

135 dissection or rupture that was not present at initial presentation. All operative reports of

136 AD/IMH/PAU patients and population referents were screened for aortic interventions. Medical

137 records and follow-up imaging were reviewed to identify new dissection (including progression

138 from IMH, retrograde Stanford type A dissection, new Stanford type B dissection after repair of

6

139   De Bakey type II dissection) and rupture. Only first aortic interventions, first subsequent

140   dissections or ruptures were considered. Events were analyzed as a composite endpoint (any

141   aortic event) and by event type separately.

142

143   *2.3. Assessment of new aneurysm formation*

144   To identify aneurysm formation during follow-up, available imaging was reviewed for

145   AD/IMH/PAU patients and population referents. This included any contrast or non-contrast CT

146   or MRI with visualization of the entire thoracic or abdominal aorta respectively and a slice

147   thickness of 5 mm or less. Abdominal ultrasound was included if performed for aneurysm

148   screening or, if providing satisfactory evaluation of the abdominal aorta in two planes when

149   performed for other reasons. As there was no standardized imaging assessment for

150   AD/IMH/PAU patients during the study period, imaging was at the discretion of the provider at

151   the time (frequency and sections of the aorta imaged). This usually correlated with the acuity of

152   the aortic pathology, the extent of disease, and stability over time. Population referents had no

153   standard aneurysm screening and imaging was often performed for other reasons.

154   The maximum diameter of the ascending aorta, the aortic arch, the descending and the abdominal

155   aorta was measured outer-to-outer wall perpendicular to the course of the aorta using an

156   electronic caliper. Cut off values to define an aneurysm of the thoracic aorta were based on

157   previously reported mean values for normal thoracic aortic diameters.[20] Mean normal diameters

158   in each aortic segment were multiplied by 1.5, resulting in cut off values of ≥ 4.5 cm for the

159   ascending aorta (aortic valve to innominate artery), ≥ 4 cm for the aortic arch (innominate artery

160   to left subclavian artery) and ≥ 3.7 cm for the descending aorta (left subclavian artery to

161   diaphragm). For the abdominal aorta, a generally accepted cut off value of ≥ 3 cm was used to

162   define an aneurysm.[21] Any first-time aneurysm formation, associated or not associated with the

7

163 initial AD/IMH/PAU pathology, was noted. If no aneurysm formation was documented, subjects

164 were censored on the date of the last available imaging or at death. Subjects with known or

165 repaired aneurysm prior to AD/IMH/PAU diagnosis (or the index date in referents) were

166 excluded from the analysis as were those with no available follow-up imaging. For excluded

167 AD/IMH/PAU patients, matched population referents were excluded likewise to maintain the age

168 and sex-matching; for excluded referents, their matched AD/IMH/PAU patient was excluded

169 only if all three referent subjects had been excluded due to prior aneurysm or lack of imaging.

170 Due to the variation in the availability of thoracic and abdominal imaging, analysis was

171 performed for thoracic and abdominal aneurysm formation separately.

172

173 *2.4. Statistical analysis*

174 Summary statistics including mean (standard deviation) or median (range), and frequencies

175 (percent) were used to describe baseline characteristics and descriptive outcomes. Univariate

176 associations of baseline characteristics between AD/IMH/PAU patients and population referents

177 were made using Student's t-test for continuous and χ^2 test for categorical variables with Fisher's

178 exact test for low frequency events. Subtypes AD, IMH, and PAU were compared using ANOVA

179 for continuous variables and χ^2 test for categorical variables. Endpoints were evaluated as time to

180 event using life tables and Kaplan Meier plots. Cox proportional hazards regression was used to

181 compare AD/IMH/PAU patients and population referents, adjusting for age, sex and the Charlson

182 Comorbidity Index. For all outcomes, analyses were performed in two ways: by including all

183 events from the time of diagnosis forward and by including events >14 days after diagnosis only

184 to assess for the risk of aortic events beyond the acute phase. P-values <.05 were considered

185 significant. Statistical analyses were performed using STATA (StataCorp., College Station, TX)

186 and SAS software (SAS Institute Inc., Cary, NC).

187

188   The study was approved by the Institutional Review Boards of the two major health care

189   providers in the REP, Mayo Clinic and Olmsted Medical Center. All individuals included in the

190   study had already provided informed consent for the use of their medical records in research as

191   part of the REP.[16]

192

193   **3. Results**

194   One-hundred and thirty-three AD/IMH/PAU patients were identified; 77 had AD, 21 IMH, and

195   35 PAU. Mean age at diagnosis was 71.8 years (SD 14.1) and 57% were male. Baseline

196   characteristics of the AD/IMH/PAU cohort and population referents are displayed in **Table I**

197   (some of this data has been published before[14, 15]). Median follow-up was 10.2 years for

198   AD/IMH/PAU patients and 10.1 years for matched population referents.

199

200   *3.1. Aortic death*

201   During follow-up, 73 (55%) of 133 subjects in the AD/IMH/PAU cohort died compared to 144

202   (36%) of 399 in the referent cohort. Aortic death occurred in 23 (32%) of 73 AD/IMH/PAU

203   decedents due to rupture (n=12, 52%), complications after surgical treatment of AD/IMH/PAU

204   (n=5, 22%), ischemic complications (n=4, 17%) and unspecified aortic causes (n=2, 9%).

205   Estimated freedom from aortic death in AD/IMH/PAU patients at 5, 10, and 15 years was 84%,

206   80% and 77%. No aortic deaths occurred in population referents (adjusted HR for aortic-related

207   death in AD/IMH/PAU 184.7, 95% CI 10.3 – 3299.2, p<.001). Fifteen (11%) deaths occurred

208   within 14 days of AD/IMH/PAU diagnosis, thereof, 13 (87%) were aortic-related. Late deaths

209   (>14 days) were due to aortic causes in 10 (17%) of 58. For those surviving the first 14 days after

210 AD/IMH/PAU diagnosis, estimated freedom from aortic death at 5, 10, and 15 years was 93%,

211 85%, and 85% (adjusted HR for aortic death among AD/IMH/PAU 67.6, 95% CI 3.3 – 1401.7,

212 p=.006). Among subtypes, only AD was associated with an increased risk of aortic-related death

213 both when including and when excluding acute deaths (**Table II**, subtype analyses not adjusted

214 for the Charlson comorbidity Index due to low event numbers).

215 Other prevalent causes of death in AD/IMH/PAU patients were non-aortic cardiovascular causes

216 (n=21, 29%), cancer (n=8, 11%).[14, 15] While none of the population referents died from an aortic

217 cause, the majority also died from non-aortic cardiovascular disease (n=40, 28%) or cancer

218 (n=29, 20%). Trauma and respiratory causes accounted for 5 (3%) and 11 (8%) of deaths among

219 referents, respectively.

220

221 *3.2. Subsequent aortic events*

222 Fifty (38%) of 133 AD/IMH/PAU patients had a subsequent aortic event: 48 had at least one

223 aortic intervention (including initial treatment), 7 had new dissection, 7 had new rupture (11 had

224 more than one of these events). Estimated freedom from any aortic event at 5, 10, and 15 years

225 was 60%, 56%, and 56%. Among population referents there were 8 non-ruptured aneurysm

226 repairs but no other aortic-related events, resulting in an adjusted HR for any aortic event and

227 first aortic intervention in AD/IMH/PAU patients of 33.3 (95% CI 15.3 – 72.0, p<.001) and 31.5

228 (95% CI 14.5 – 68.4, p<.001), respectively. Survival free from aortic intervention in

229 AD/IMH/PAU patients and referents and is displayed in **Fig 1**. Freedom from new rupture and

230 dissection in AD/IMH/PAU patients is displayed in **Fig 2**.

231 Thirty-six (75%) of 48 aortic interventions and 2 (29%) of 7 new ruptures in AD/IMH/PAU

232 patients occurred within 14 days of diagnosis. No new dissections occurred in the acute phase.

233   When excluding acute interventions and events ≤14 days, AD/IMH/PAU patient remained at

234   increased risk for any aortic event (adjusted HR 10.8, 95% CI 3.9 – 29.8, p<.001) and first aortic

235   intervention (adjusted HR 9.6, 95% CI 3.4 – 26.8, p<.001) when compared to population

236   referents.

237   Unadjusted subtype analyses showed an increased risk of any aortic event and intervention for

238   AD and IMH, both when including the acute phase and beyond that. PAU alone was associated

239   with aortic events only when including acute phase events but not thereafter (**Table II**).

240

241   *3.3. New aneurysm formation*

242   After exclusion of subjects with prior known or repaired thoracic aneurysm (**Table I**) as well as

243   those without imaging, a total of 69 AD/IMH/PAU patients (40 AD, 11 IMH, and 18 PAU) and

244   103 population referents remained for the assessment of thoracic aneurysm formation. Estimated

245   freedom of first-time diagnosis of a thoracic aneurysm at 5, 10, and 15 years was 42%, 37%, and

246   25% in AD/IMH/PAU patients versus 96%, 88%, and 75% in population referents (adjusted HR

247   10.9, 95% CI 5.4 – 21.7, p <.0001; **Fig 3a**). Among those AD/IMH/PAU patients who did not

248   develop a thoracic aneurysm within 14 days of AD/IMH/PAU diagnosis, freedom of thoracic

249   aneurysm formation at 5, 10, and 15 years was 78%, 70%, 46% (adjusted HR 6.2, 95% CI 1.8 –

250   21.1, p=.004; **Fig 3b**).

251   For the assessment of abdominal aneurysm formation, 77 AD/IMH/PAU patients (40 AD, 18

252   IMH, and 19 PAU) and 131 population referents remained. Estimated freedom of first-time

253   diagnosis of an abdominal aneurysm at 5, 10, and 15 years was 56%, 44%, and 44% in

254   AD/PAU/IMH patients versus 93%, 86%, and 86% in population referents (adjusted HR 8.3,

255   95% CI 4.1 – 16.7, p<.001; **Fig 4a**). Among those who did not have an abdominal aneurysm

11

256 within 14 days of AD/IMH/PAU diagnosis, freedom of abdominal aneurysm formation at 5, 10,

257 and 15 years was 82%, 65%, 65% (adjusted HR 2.8, 95% CI 1.0 – 7.6, p=.040; **Fig 4b**).

258

259 **4. Discussion**

260 This assessment of newly diagnosed AD, IMH, and PAU patients in Olmsted County, MN from

261 1995-2015 quantifies aortic-related outcomes from a population-based approach. Our results

262 confirm the significant risk of aortic events known to be associated with AD/IMH/PAU diagnosis

263 in the short-term. However, our findings also highlight the relevant risk of aortic death and

264 subsequent aortic events that remains in these patients >14 days after diagnosis. Despite follow-

265 up and treatment, the long-term prognosis of these pathologies remains poor and never

266 approximates population levels.

267 We have previously shown that AD/IMH/PAU patients remain at a significantly increased risk of

268 all-cause mortality when surviving the first 14 days after diagnosis.[14] In our cohort, deaths were

269 due to aortic causes in 32%, representing the most common cause of death. The majority (52%)

270 of aortic deaths were due to rupture. Although most common within 14 days of diagnosis, aortic

271 death remained a significant risk thereafter, accounting for 17% of late deaths, resulting in an

272 estimated freedom from aortic death at 5, 10, and 15 years of 84%, 80% and 77%. In previous

273 reports, mostly including patients with aortic dissection, late deaths were due to aortic causes in

274 16 – 39% [6-8] and freedom from aortic death at 5 and 10 years (85% and 82%) was similar to our

275 series.[22] Chou et al. reported 32% aortic or possibly aortic-related late deaths in patients with

276 IMH or PAU.[10] Looking at subtypes in our cohort, the risk of aortic death was mainly driven by

277 AD, with few late aortic deaths among IMH and PAU patients. Whereas in Chou's series, all

278 patients presented acutely, our cohort included newly diagnosed AD, IMH, and PAU pathologies

279 regardless of acuity, thus possibly including more patients with less aggressive aortic disease. As

280 we have previously shown, mortality has not improved over the past 20 years and aortic death

281 remains one of the most important causes of death in long-term.[14] If the prognosis of

282 AD/IMH/PAU is to be improved, advances in the long-term treatment and follow-up of these

283 patients are clearly necessary.

284 Similar to aortic death, subsequent aortic events were most prevalent within 14 days of

285 AD/IMH/PAU diagnosis and the most frequent subsequent aortic event was aortic intervention.

286 This included initial surgical treatment of AD, IMH, or PAU, explaining the early drop in the

287 Kaplan Meier curve (**Fig 1**). After excluding acute events (≤14 days), AD/IMH/PAU patients

288 remained at significantly increased risk for any subsequent aortic event, in particular during the

289 first five years post diagnosis. When compared to population referents, the risk of ever

290 undergoing an aortic intervention among those who survived the acute phase without surgical

291 treatment remained ten-fold higher with a total of 14% of these patients eventually undergoing

292 intervention. Kret et al. reported 38% of medically treated patients with type B dissections

293 eventually needing surgery in their series, while overall follow-up compliance of patients was

294 limited.[13] Chou et al. reported 43% of IMH and 30% of PAU patients undergoing late surgery.[10]

295 In our cohort, AD and IMH accounted for the majority of subsequent interventions. Patients with

296 PAU not requiring surgery within the first 14 days, had the same low long-term risk of aortic

297 intervention as the general population. However, due to low event rates among AD, IMH, and

298 PAU separately, subtype analyses have to be interpreted very cautiously.

299 The assessment of aneurysm formation was clearly limited by the availability of follow-up

300 imaging and was subdivided into thoracic and abdominal aneurysm formation for the same

301 reason. The initial drop in survival free from first-time thoracic and abdominal aneurysm in

302 AD/IMH/PAU patients (**Fig 2**) has to be considered in the context that the data reflects the first

303 time patients were diagnosed with an aneurysm on imaging. Due to the lack of imaging

304 immediately prior to the AD/IMH/PAU event in most patients, aneurysm formation was often

305 first diagnosed at the same time as AD, IMH, or PAU and it remains unclear whether aneurysm

306 or the AD/IMH/PAU pathology came first. However, when excluding those diagnosed with

307 aneurysm formation within 14 days, the risk of developing any first-time aneurysm remained 6.2-

308 fold and 2.8-fold higher than in population referents for the thoracic and abdominal aorta

309 respectively. It has to be noted, that any first thoracic and abdominal aneurysm was documented,

310 regardless whether it involved the site of the initial AD/IMH/PAU pathology or not. These data

311 may therefore also reflect "systemic aortic disease"[2], meaning that, in these patients with

312 pathologies of the aortic media, the entire aorta is predisposed to aneurysm formation.

313 It has to be kept in mind that this AD/IMH/PAU incident cohort includes all newly diagnosed

314 patients with these pathologies. As mentioned above, it may include less severe findings than

315 series from referral centers. This may particularly be true for PAU patients, which more often

316 than AD and IMH, were chronic or of unknown acuity. The primary aim of this study was to

317 define aortic-related outcomes in AD, IMH, and PAU from a broader perspective. Therefore, all

318 identified pathologies were included, considering their common pathological disruption of the

319 media layer of the aorta. Furthermore, those presenting with a pathology of unknown acuity may

320 not necessarily have been asymptomatic but may have had atypical or not explicitly remembered

321 symptoms. This comprehensive approach may explain somewhat lower rates of aortic deaths and

322 subsequent aortic events than reported in single center series but may more likely reflect true

323 outcomes in the AD/IMH/PAU population overall.

324 When comparing AD, IMH, and PAU patients to population referents, it is obvious that the latter

325 will be at much smaller risk for any aortic event. However, specific risks of AD/IMH/PAU

326 patients to suffer an aortic-related complication may be difficult to grasp without a baseline in the

327 general population. Thus, the present study stresses the implications of the aortic pathologies AD,

328 IMH, and PAU on the further clinical course of affected patients.

329 The REP provides a reliable infrastructure for population-based research in Olmsted County,

330 capturing virtually all health care provided to the residents of this geographically isolated region.

331 Patients are followed across providers and death certificates as well as autopsy reports are made

332 available through the database. These are unique conditions within the United States. While this

333 population-based strategy strengthens our study, there are some limitations to the generalizability

334 of the study findings. The demographical characteristic of Olmsted County, reflect a

335 predominantly white population that is slightly healthier than Minnesota state residents overall.[14]

336 However, prior studies have shown high similarity in terms of age, sex, and ethnic characteristics

337 between Olmsted County and Minnesota/upper Midwest residents as well as similar mortality

338 rates for Olmsted County and the United States overall.[23]

339

340 **5. Conclusion**

341 The findings of this study highlight the high risk of aortic death, subsequent aortic events and

342 aneurysm formation that is associated with AD/IMH/PAU diagnosis. Most importantly, even in

343 patients who survive the first 14 days after diagnosis without one of these complications, a

344 substantial aortic risk persists. This strengthens the need for further improvements in the care and

345 treatment of these patients, potentially advocating for more rigorous follow-up in post diagnosis

346 aortic care and modalities of treatment for these patients. The question of how and to what extent

347 adverse aortic outcomes can be prevented most effectively remains to be the subject of further

348 research, but clearly, room exists for improvement.

15

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Tables

Table I: Baseline characteristics of the AD/IMH/PAU cohort and population referents

	Referents (n=399)	AD/IMH/PAU (n=133)	p[*]	AD/IMH/PAU Subtypes			p
				AD (n=77)	IMH (n=21)	PAU (n=35)	
Age (years), mean (SD)	71.8 (14.1)	71.8 (14.1)	1.0	68.9 (15.6)	73.5 (11.5)	77.1 (10.0)	.015
Male gender	76 (57.1%)	76 (57.1%)	1.0	46 (59.7%)	11 (52.4%)	19 (54.3%)	.770
Charlson Comorbidity Index, mean (SD)	1.7 (2.1)	2.6 (2.6)	<.001	2.1 (2.2)	2.8 (2.6)	3.7 (3.2)	.006
Thoracic aneurysm							
Prior known	5 (1.2%)	11 (8.3%)	<.001	6 (7.8%)	2 (9.5%)	3 (8.6%)	.912
Prior repair	2 (0.5%)	2 (1.5%)	<.001	1 (1.3%)	1 (4.8%)	0 (0%)	.359
Abdominal aneurysm							
Prior known	7 (1.7%)	6 (4.5%)	.100	3 (3.9%)	0 (0%)	3 (8.6%)	.423
Prior repair	3 (0.7%)	11 (8.3%)	<.001	6 (7.8%)	1 (4.8%)	4 (11.4%)	.677
Acuity of presentation[†]			-				<.001
Acute	-	79 (59.4%)		52 (67.5%)	17 (81.0%)	10 (28.6%)	
Subacute	-	4 (3.0%)		2 (2.6%)	1 (4.8%)	1 (2.9%)	
Chronic	-	3 (2.3%)		2 (2.6%)	0 (0%)	1 (2.9%)	
Unknown	-	47 (35.3)		21 (27.3%)	3 (14.3%)	23 (65.7%)	
Stanford classification			-				<.001
Type A	-	-		45 (58.4%)	5 (23.8%)	-	
Type B	-	-		32 (41.6%)	16 (76.2%)	-	
De Bakey classification			-				-
Type I	-	-		24 (31.2%)	-	-	
Type II	-	-		21 (27.3%)	-	-	
Type IIIa	-	-		8 (10.4%)	-	-	
Type IIIb	-	-		24 (31.2%)	-	-	
Anatomic localisation							-
Thoracic	-	-		-	-	18 (51.4%)	
Abdominal	-	-		-	-	17 (48.6%)	
Connective tissue disease	-	8 (6.0%)	-	8 (10.4%)	0 (0.0%)	0 (0.0%)	.052
Bicuspid aortic valve	-	3 (2.3%)	-	1 (1.3%)	1 (4.8%)	1 (2.9%)	.388
Iatrogenic	-	7 (5.3%)	-	6 (7.8%)	1 (4.8%)	0 (0.0%)	.281

[*]p-values for comparisons between the AD/IMH/PAU and the referent cohort do not acoount for matching

[†]Acute: ≤14 days of symptom onset; subacute: 15-90 days; chronic: >90 days

Table II: Risk of aortic death in AD/IMH/PAU patients versus matched population referents.

	All AD/IMH/PAU patients (n=133)											
	All events						**Excluding acute events***					
	AD/IMH/PAU		**Referents**		**AD/IMH/PAU vs. referents**		**AD/IMH/PAU**		**Referents**		**AD/IMH/PAU vs. referents**	
	At risk	Events	At risk	Events	HR (95% CI)	p	At risk	Events	At risk	Events	HR (95% CI)	p
Aortic death	133	23	399	0	184.7 (10.3 – 3299.2)	<.001	118	10	354	0	67.6 (3.3 – 1401.7)	.006
Any aortic event	133	50	399	8	33.3 (15.3 – 72.0)	<.001	83	13	249	6	10.8 (3.9 – 29.8)	<.001
Aortic intervention	133	48	399	8	31.5 (14.5 – 68.4)	<.001	83	12	249	6	9.6 (3.4 – 26.8)	<.001
	Aortic dissection (AD, n=77)[†]											
Aortic death	77	16	231	0	111.7 (6.1 – 2030.6)	.001	65	5	195	0	33.9 (1.4 – 801.1)	.029
Any aortic event	77	34	231	4	47.6 (16.4 – 137.8)	<.001	39	7	117	2	18.2 (3.5 – 94.2)	<.001
Aortic intervention	77	33	231	4	44.8 (15.5 – 130.0)	<.001	39	6	117	2	14.9 (2.8 – 79.1)	.002
	Intramural hematoma (IMH, n=21)[†]											
Aortic death	21	4	63	0	30.5 (1.2 – 769.2)	.038	20	3	60	0	23.6 (0.8 – 669.9)	.064
Any aortic event	21	9	63	3	14.5 (3.8 – 55.0)	<.001	16	5	48	3	7.3 (1.7 – 31.7)	.008
Aortic intervention	21	9	63	3	14.5 (3.8 – 55.0)	<.001	16	5	48	3	7.3 (1.7 – 31.7)	.008
	Penetrating aortic ulcer (PAU, n=35)[†]											
Aortic death	35	3	105	0	28.4 (0.9 – 878.7)	.055	33	2	99	0	17.5 (0.4 – 696.6)	.127
Any aortic event	35	7	105	1	24.5 (3.0 – 199.9)	.003	28	1	84	1	3.2 (0.2 – 51.8)	.408
Aortic intervention	35	6	105	1	21.2 (2.5 – 176.6)	.005	28	1	84	1	3.2 (0.2 – 51.8)	.408

[*]Including deaths >14 days of diagnosis only; [†]unadjusted for the Charlson Comorbidity Index due to low event numbers per subtype

1 **Figure legends**

2

3 **Fig 1.** Survival free from aortic intervention for AD/IMH/PAU patients versus population

4 referents of similar age and gender.

5

6 **Fig 2.** Survival free from aortic rupture **(a)**, and survival free from new aortic dissection **(b)** after
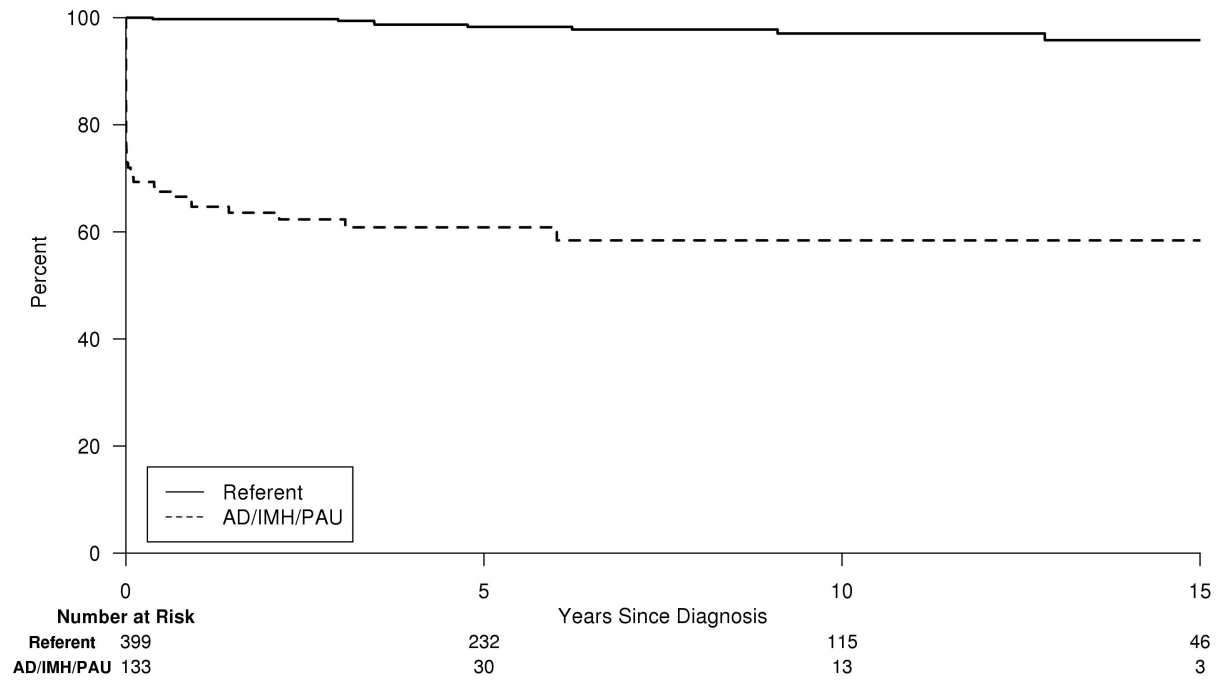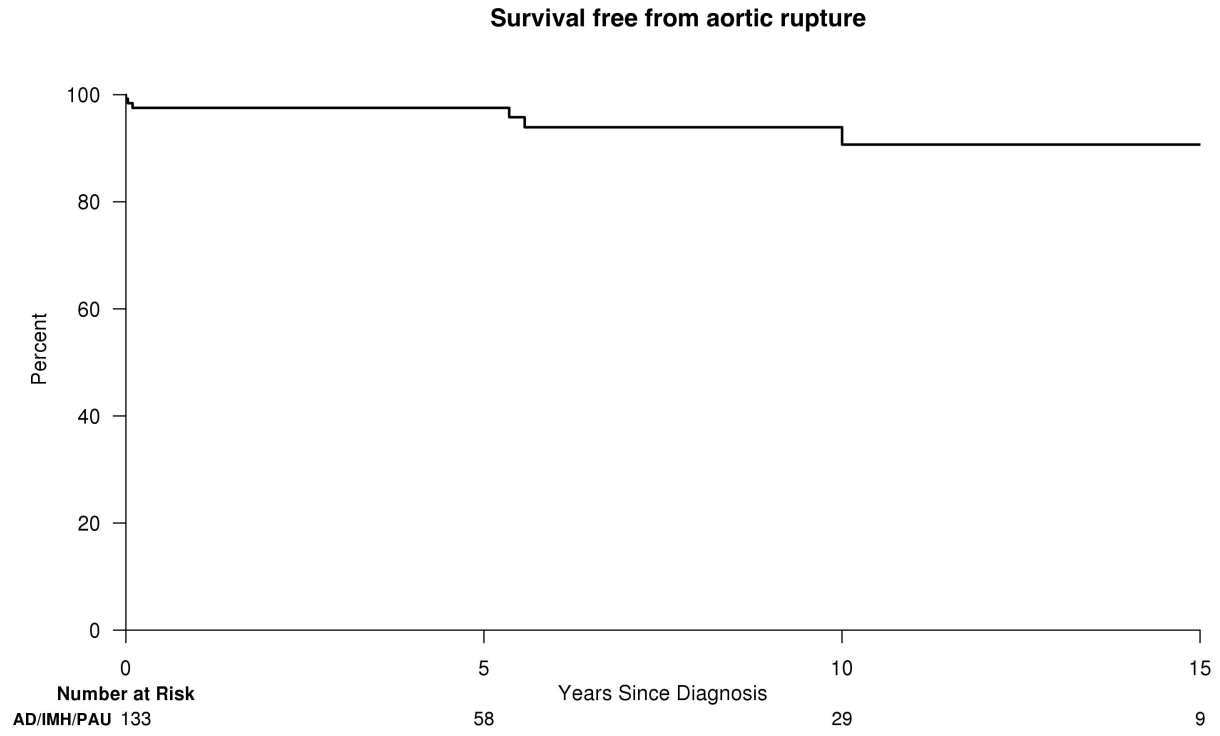
7 diagnosis of AD, IMH, or PAU.

8

9 **Fig 3.** Survival free from first time diagnosis of a thoracic aneurysm for AD/IMH/PAU

10 patients versus population referents of similar age and gender, including all detected

11 aneurysms from the time of AD/IMH/PAU diagnosis **(a)** and those > 14 days after diagnosis
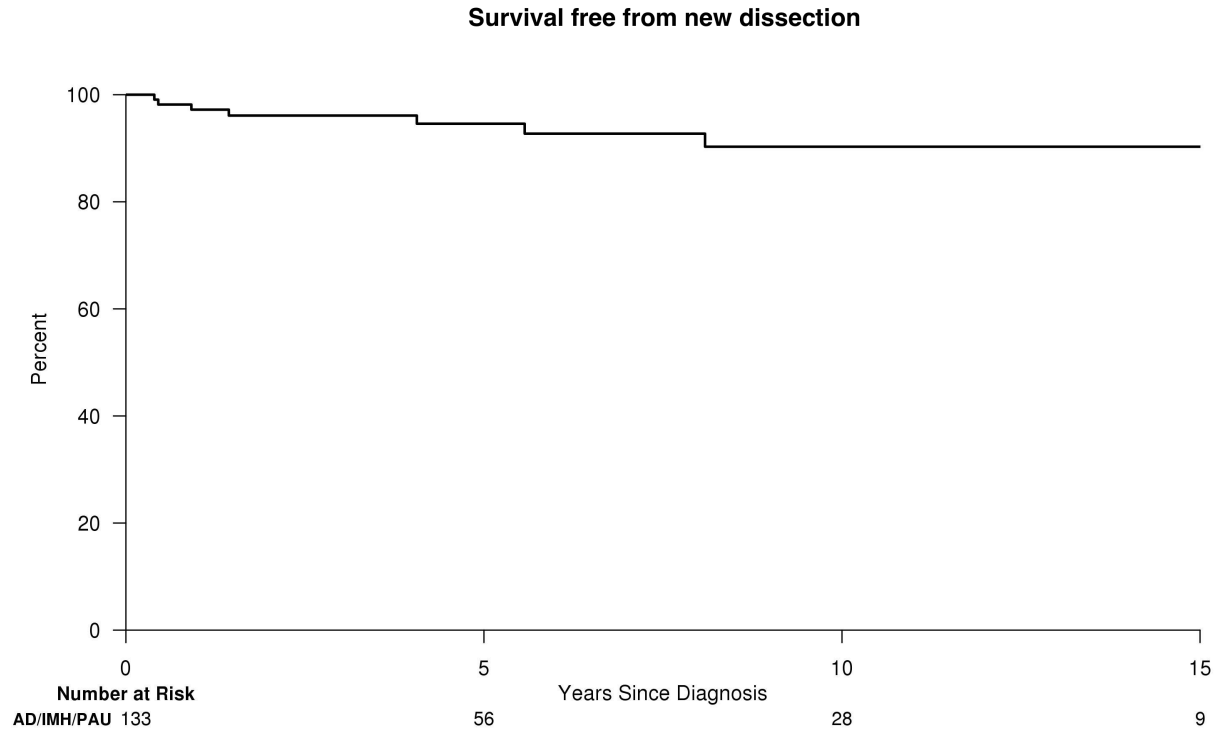
12 only **(b).**

13

14 **Fig 4.** Survival free from first time diagnosis of an abdominal aneurysm for AD/IMH/PAU patients

15 versus population referents of similar age and gender, including all detected aneurysms from the time

16 of AD/IMH/PAU diagnosis **(a)** and those > 14 days after diagnosis only **(b).**
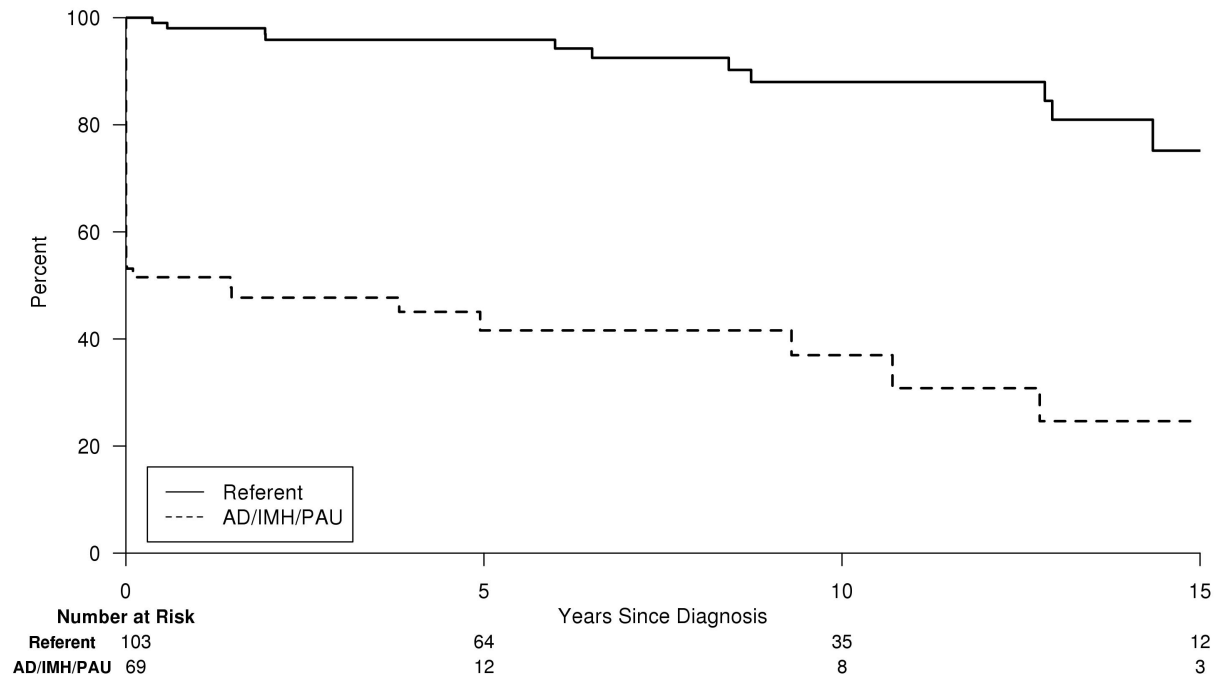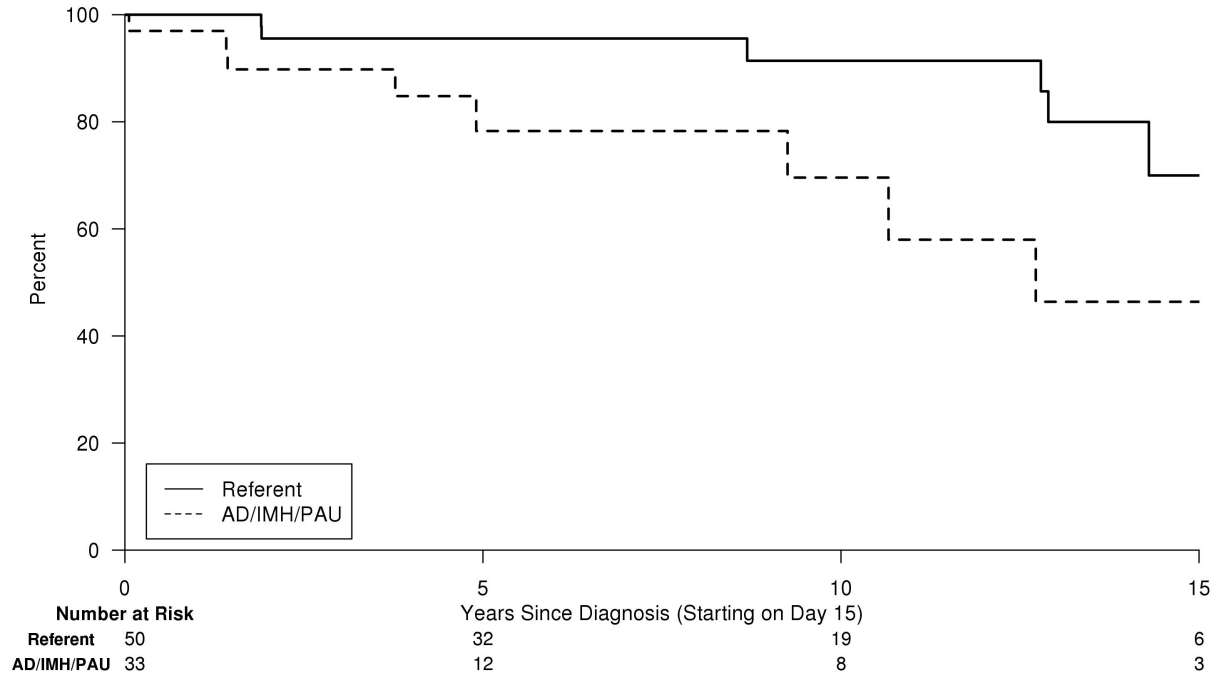
Survival free from aortic intervention

Number at Risk			
Referent 399	232	115	46
AD/IMH/PAU 133	30	13	3

Survival free from aortic rupture

Percent

Years Since Diagnosis

Number at Risk

AD/IMH/PAU 133   58   29   9

Survival free from new dissection

Percent

Number at Risk
AD/IMH/PAU 133   56   28   9

Years Since Diagnosis

Survival free from first time diagnosis of a thoracic aortic aneurysm

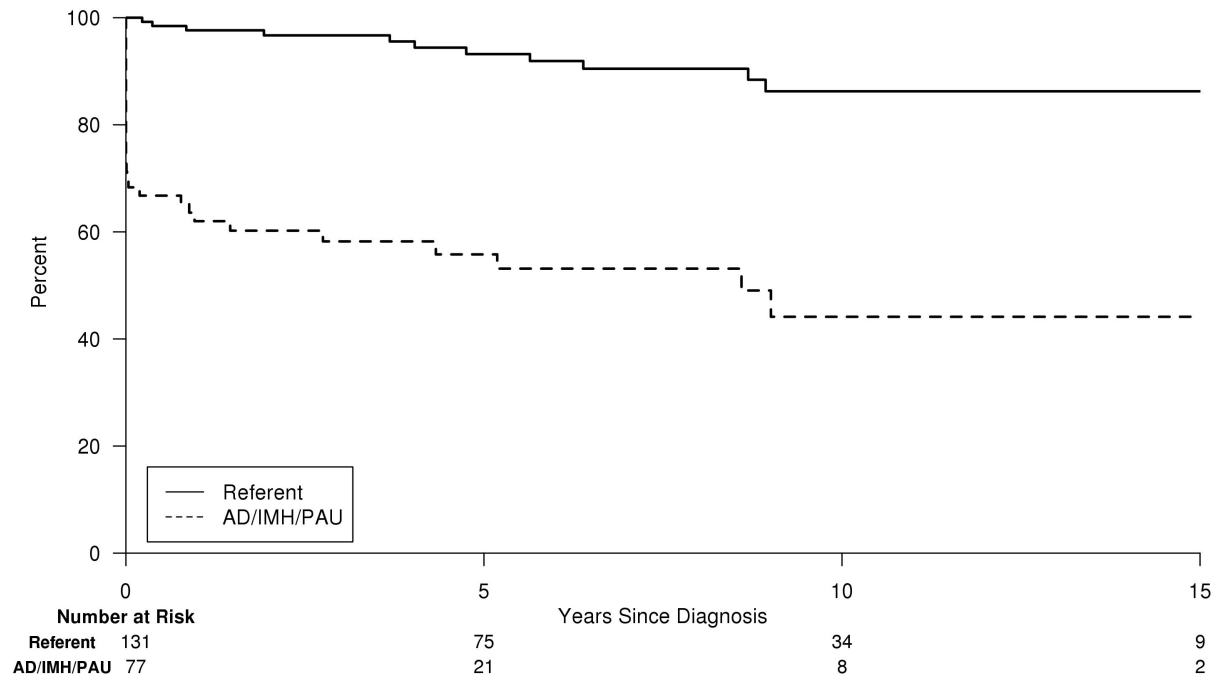| Number at Risk				
Referent	103	64	35	12
AD/IMH/PAU	69	12	8	3

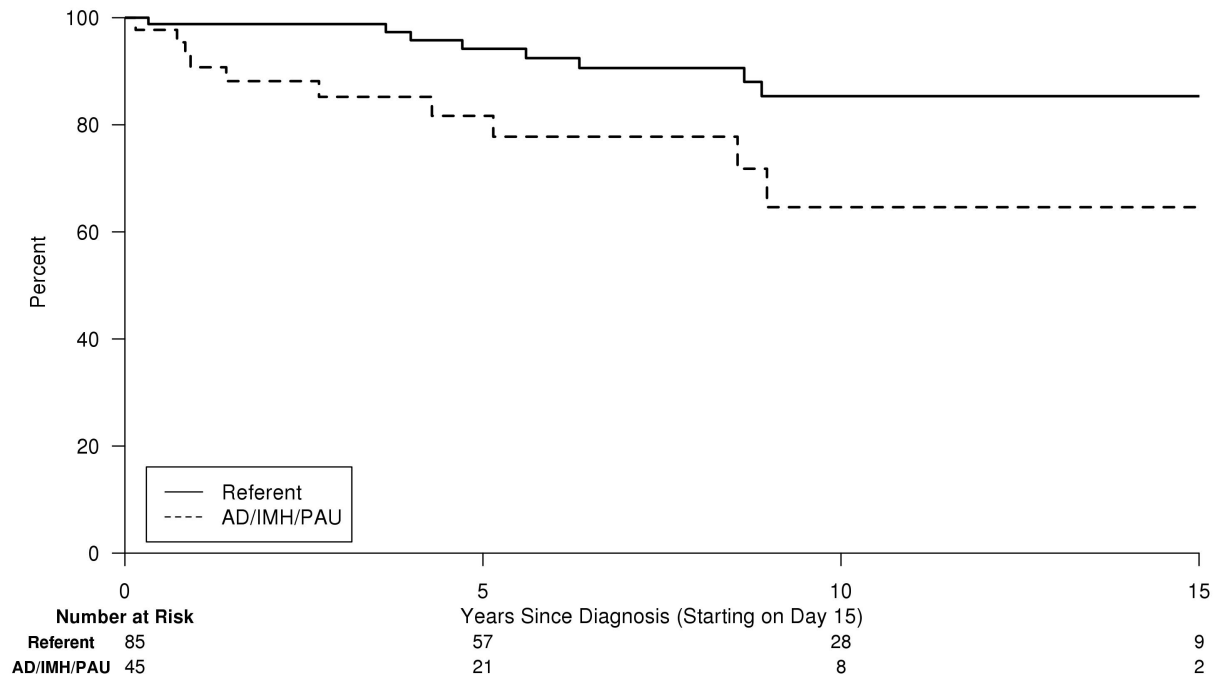**Survival free from first time diagnosis of a thoracic aortic aneurysm**

Survival free from first time diagnosis of an abdominal aortic aneurysm

Percent

Years Since Diagnosis

Number at Risk				
Referent	131	75	34	9
AD/IMH/PAU	77	21	8	2

Legend:
— Referent
- - - AD/IMH/PAU

Survival free from first time diagnosis of an abdominal aortic aneurysm