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

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23 Abstract

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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 28 County, MN from 1995-2015. Primary end-point was aortic death. Secondary end-points were 29 subsequent aortic events (aortic intervention, new dissection or rupture not present at 30 presentation) and first-time diagnosis of an aortic aneurysm. Outcomes were compared to 31 randomly selected population referents matched for age and sex in a 3:1 ratio using Cox 32 proportional hazards regression adjusting for comorbidities. 33 Results: Among 133 patients (77 AD, 21 IMH, 35 PAU), 57% were male and mean age was 71.8 34 years (SD 14). Median follow-up was 10 years. Of 73 deaths among AD/IMH/PAU patients, 23 35 36 (32%) were aortic-related. Estimated freedom from aortic death was 84%, 80% and 77% at 5, 10, 37 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 38 patients had a subsequent aortic event (aortic intervention, new dissection or rupture) while there 39 were eight (2%) aortic events among population referents (all elective aneurysm repairs; adjusted 40 41 HR for any aortic event and aortic intervention in AD/IMH/PAU patients 33.3, 95% CI 15.3 -42 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 43 any aortic event (adjusted HR 10.8, 95% CI 3.9 – 29.8, p<.001) and aortic intervention (adjusted 44 HR 9.6, 95% CI 3.4 – 26.8, p<.001). Among those subjects with available follow-up imaging, the 45 risk of first-time diagnosis of aortic aneurysm was significantly increased for AD/IMH/PAU 46

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	
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67 **Disclosures:** None.

68 **1. Introduction**

Aortic dissection (AD), intramural hematoma (IMH) and penetrating aortic ulcer (PAU) are 69 dreaded aortic pathologies. Despite the distinct characteristics of each of these entities, they all 70 involve a disruption of the media layer of the aortic wall and may progress from one to another,¹ 71 sharing a significant risk of acute and chronic aortic-related morbidity and mortality.² For acute 72 Stanford type A and type B dissection, the International Registry of Acute Aortic Dissection 73 (IRAD) reported an in-hospital mortality of 22% and 14% respectively.³ At three years, almost 74 25% of those with type B dissection discharged alive will additionally have died.⁴ In both, type A 75 and type B dissection, aortic events are the most common cause of death.⁵⁻⁸ Acute survival of 76 patients presenting with IMH and PAU may be slightly better than for those with AD (9-13%)^{9,10} 77 but poor long-term survival has been reported in an institutional series.¹⁰ Additionally, patients 78 with chronic AD, IMH, and PAU carry a significant risk of subsequent aortic events including 79 recurrent dissection, rupture, and aneurysmal degeneration, often requiring intervention. 80 81 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 centers⁴, 82 ¹⁰⁻¹² and may be biased by limited follow-up compliance of these patients¹³ and lack of mortality 83 data. 84 We have previously characterized the incidence of AD, IMH, and PAU and its associated 85 86 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 87 cardiovascular events.¹⁵ The objective of the present study was to quantify the risk of aortic 88

- death, subsequent aortic events, and aortic aneurysm formation after AD, IMH, and PAU. By
- 90 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

The detailed identification process of the incidence cohort we assessed is described elsewhere.^{14,} 95 ¹⁵ In brief, we utilized the resources of the REP, a unique collaboration of health care providers 96 linking together medical records of virtually all residents of Olmsted County, MN.^{16, 17} This 97 98 permits the identification of incident diagnoses at a population level and allows follow-up of patients across providers. Within the REP, adult residents (≥ 18 years of age) with a new 99 diagnosis of AD, IMH, or PAU from 1995-2015 were identified using International Classification 100 of Disease codes (ICD, 9th and 10th revision) and Hospital Adaptation of the International 101 Classification of Diseases codes (HICDA, 2nd edition). Study inclusion required imaging 102 confirmation of the diagnosis. For immediate decedents, AD/IMH/PAU had to be confirmed by 103 autopsy or be the primary diagnosis on the death certificate. AD, IMH, and PAU were defined 104 based on standard criteria used in current guidelines¹ and classified as acute (<14 days of 105 symptom onset), subacute (15 - 90 days), chronic (>90 days), or unknown presentation 106 (unknown date of onset of the pathology). AD was classified using the De Bakey and the 107 Stanford classification, while IMH was classified using the Stanford classification only. PAU was 108 109 classified by anatomic location.

The AD/IMH/PAU cohort was compared to randomly selected Olmsted County population
referents matched for age and sex. As previously described, a matching ratio of 3:1 was chosen
based on a sample size calculation to detect a minimum hazard ratio (HR) for all-cause death of
1.95 with an alpha of 0.05 and power of 0.8.¹⁴ For population referents, the diagnosis date of the
matched AD/IMH/PAU patient was set as the index date to differentiate pre-existing conditions

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

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

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

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.

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121 2.1. Assessment of aortic death

122 Primary endpoint was aortic death. Dates and causes of death were obtained from death certificates available through the REP, which collates up to date information on in state and out 123 of state deaths from multiple sources.¹⁷ For a minority of subjects with missing vital status 124 information (e.g. due to migration), an institutionally approved Internet research location service 125 (Accurint, www.accurint.com) was used and death certificates requested where permissible as per 126 state laws. For three AD/IMH/PAU patients and three population referents known to have died 127 128 out of state, deaths certificates could not be obtained. Causes of death retrieved from death certificates were cross-checked with medical records. Aortic death was defined as death due to 129 rupture, ischemic complications, surgical complications related to AD/IMH/PAU treatment, and 130 other aortic-related causes (not specified). 131

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133 2.2. Assessment of subsequent aortic events

The secondary end-point of a subsequent aortic event included aortic intervention, and new dissection or rupture that was not present at initial presentation. All operative reports of AD/IMH/PAU patients and population referents were screened for aortic interventions. Medical records and follow-up imaging were reviewed to identify new dissection (including progression from IMH, retrograde Stanford type A dissection, new Stanford type B dissection after repair of

De Bakey type II dissection) and rupture. Only first aortic interventions, first subsequent
dissections or ruptures were considered. Events were analyzed as a composite endpoint (any
aortic event) and by event type separately.

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143 2.3. Assessment of new aneurysm formation

To identify aneurysm formation during follow-up, available imaging was reviewed for 144 AD/IMH/PAU patients and population referents. This included any contrast or non-contrast CT 145 146 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 screening or, if providing satisfactory evaluation of the abdominal aorta in two planes when 148 performed for other reasons. As there was no standardized imaging assessment for 149 AD/IMH/PAU patients during the study period, imaging was at the discretion of the provider at 150 the time (frequency and sections of the aorta imaged). This usually correlated with the acuity of 151 the aortic pathology, the extent of disease, and stability over time. Population referents had no 152 153 standard aneurysm screening and imaging was often performed for other reasons. The maximum diameter of the ascending aorta, the aortic arch, the descending and the abdominal 154 aorta was measured outer-to-outer wall perpendicular to the course of the aorta using an 155 electronic caliper. Cut off values to define an aneurysm of the thoracic aorta were based on 156 previously reported mean values for normal thoracic aortic diameters.²⁰ Mean normal diameters 157 in each aortic segment were multiplied by 1.5, resulting in cut off values of \geq 4.5 cm for the 158 ascending aorta (aortic valve to innominate artery), ≥ 4 cm for the aortic arch (innominate artery) 159 to left subclavian artery) and ≥ 3.7 cm for the descending aorta (left subclavian artery to 160 diaphragm). For the abdominal aorta, a generally accepted cut off value of ≥ 3 cm was used to 161 define an aneurysm.²¹ Any first-time aneurysm formation, associated or not associated with the 162

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).

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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

- 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
- both when including and when excluding acute deaths (**Table II**, subtype analyses not adjusted
- for the Charlson comorbidity Index due to low event numbers).
- Other prevalent causes of death in AD/IMH/PAU patients were non-aortic cardiovascular causes (n=21, 29%), cancer (n=8, 11%).^{14, 15} While none of the population referents died from an aortic cause, the majority also died from non-aortic cardiovascular disease (n=40, 28%) or cancer (n=29, 20%). Trauma and respiratory causes accounted for 5 (3%) and 11 (8%) of deaths among referents, respectively.
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221 *3.2. Subsequent aortic events*

Fifty (38%) of 133 AD/IMH/PAU patients had a subsequent aortic event: 48 had at least one 222 223 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 was 60%, 56%, and 56%. Among population referents there were 8 non-ruptured aneurysm 225 repairs but no other aortic-related events, resulting in an adjusted HR for any aortic event and 226 first aortic intervention in AD/IMH/PAU patients of 33.3 (95% CI 15.3 – 72.0, p<.001) and 31.5 227 228 (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 dissection in AD/IMH/PAU patients is displayed in Fig 2. 230 Thirty-six (75%) of 48 aortic interventions and 2 (29%) of 7 new ruptures in AD/IMH/PAU 231

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

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

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- increased risk for any aortic event (adjusted HR 10.8, 95% CI 3.9 29.8, p<.001) and first aortic 234 intervention (adjusted HR 9.6, 95% CI 3.4 – 26.8, p<.001) when compared to population 235 236 referents. Unadjusted subtype analyses showed an increased risk of any aortic event and intervention for 237 238 AD and IMH, both when including the acute phase and beyond that. PAU alone was associated with aortic events only when including acute phase events but not thereafter (Table II). 239 240 3.3. New aneurysm formation 241 After exclusion of subjects with prior known or repaired thoracic aneurysm (Table I) as well as 242 those without imaging, a total of 69 AD/IMH/PAU patients (40 AD, 11 IMH, and 18 PAU) and 243 244 103 population referents remained for the assessment of thoracic aneurysm formation. Estimated freedom of first-time diagnosis of a thoracic aneurysm at 5, 10, and 15 years was 42%, 37%, and 245 25% in AD/IMH/PAU patients versus 96%, 88%, and 75% in population referents (adjusted HR 246 10.9, 95% CI 5.4 – 21.7, p <.0001; Fig 3a). Among those AD/IMH/PAU patients who did not 247 develop a thoracic aneurysm within 14 days of AD/IMH/PAU diagnosis, freedom of thoracic 248 aneurysm formation at 5, 10, and 15 years was 78%, 70%, 46% (adjusted HR 6.2, 95% CI 1.8 -249 250 21.1, p=.004; Fig 3b). For the assessment of abdominal aneurysm formation, 77 AD/IMH/PAU patients (40 AD, 18 251 IMH, and 19 PAU) and 131 population referents remained. Estimated freedom of first-time 252 diagnosis of an abdominal aneurysm at 5, 10, and 15 years was 56%, 44%, and 44% in 253 AD/PAU/IMH patients versus 93%, 86%, and 86% in population referents (adjusted HR 8.3, 254
- 255 95% CI 4.1 – 16.7, p<.001; Fig 4a). Among those who did not have an abdominal aneurysm

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

This assessment of newly diagnosed AD, IMH, and PAU patients in Olmsted County, MN from 1995-2015 quantifies aortic-related outcomes from a population-based approach. Our results confirm the significant risk of aortic events known to be associated with AD/IMH/PAU diagnosis in the short-term. However, our findings also highlight the relevant risk of aortic death and subsequent aortic events that remains in these patients >14 days after diagnosis. Despite followup and treatment, the long-term prognosis of these pathologies remains poor and never approximates population levels.

We have previously shown that AD/IMH/PAU patients remain at a significantly increased risk of 267 all-cause mortality when surviving the first 14 days after diagnosis.¹⁴ In our cohort, deaths were 268 due to aortic causes in 32%, representing the most common cause of death. The majority (52%) 269 270 of aortic deaths were due to rupture. Although most common within 14 days of diagnosis, aortic death remained a significant risk thereafter, accounting for 17% of late deaths, resulting in an 271 estimated freedom from aortic death at 5, 10, and 15 years of 84%, 80% and 77%. In previous 272 reports, mostly including patients with aortic dissection, late deaths were due to aortic causes in 273 $16 - 39\%^{6-8}$ and freedom from a rtic death at 5 and 10 years (85% and 82%) was similar to our 274 series.²² Chou et al. reported 32% aortic or possibly aortic-related late deaths in patients with 275 IMH or PAU.¹⁰ Looking at subtypes in our cohort, the risk of aortic death was mainly driven by 276 AD, with few late aortic deaths among IMH and PAU patients. Whereas in Chou's series, all 277 patients presented acutely, our cohort included newly diagnosed AD, IMH, and PAU pathologies 278 279 regardless of acuity, thus possibly including more patients with less aggressive aortic disease. As

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

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remains one of the most important causes of death in long-term.¹⁴ If the prognosis of 281 AD/IMH/PAU is to be improved, advances in the long-term treatment and follow-up of these 282 patients are clearly necessary. 283 Similar to aortic death, subsequent aortic events were most prevalent within 14 days of 284 AD/IMH/PAU diagnosis and the most frequent subsequent aortic event was aortic intervention. 285 This included initial surgical treatment of AD, IMH, or PAU, explaining the early drop in the 286 287 Kaplan Meier curve (**Fig 1**). After excluding acute events (≤14 days), AD/IMH/PAU patients remained at significantly increased risk for any subsequent aortic event, in particular during the 288 first five years post diagnosis. When compared to population referents, the risk of ever 289 undergoing an aortic intervention among those who survived the acute phase without surgical 290 291 treatment remained ten-fold higher with a total of 14% of these patients eventually undergoing intervention. Kret et al. reported 38% of medically treated patients with type B dissections 292 eventually needing surgery in their series, while overall follow-up compliance of patients was 293 limited.¹³ Chou et al. reported 43% of IMH and 30% of PAU patients undergoing late surgery.¹⁰ 294 In our cohort, AD and IMH accounted for the majority of subsequent interventions. Patients with 295 PAU not requiring surgery within the first 14 days, had the same low long-term risk of aortic 296 297 intervention as the general population. However, due to low event rates among AD, IMH, and PAU separately, subtype analyses have to be interpreted very cautiously. 298 The assessment of aneurysm formation was clearly limited by the availability of follow-up 299 imaging and was subdivided into thoracic and abdominal aneurysm formation for the same 300

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

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

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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

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general population. Thus, the present study stresses the implications of the aortic pathologies AD, 327 IMH, and PAU on the further clinical course of affected patients. 328 The REP provides a reliable infrastructure for population-based research in Olmsted County, 329 capturing virtually all health care provided to the residents of this geographically isolated region. 330 Patients are followed across providers and death certificates as well as autopsy reports are made 331 available through the database. These are unique conditions within the United States. While this 332 population-based strategy strengthens our study, there are some limitations to the generalizability 333 334 of the study findings. The demographical characteristic of Olmsted County, reflect a predominantly white population that is slightly healthier than Minnesota state residents overall.¹⁴ 335 However, prior studies have shown high similarity in terms of age, sex, and ethnic characteristics 336 between Olmsted County and Minnesota/upper Midwest residents as well as similar mortality 337 rates for Olmsted County and the United States overall.²³ 338

339

340 **5. Conclusion**

The findings of this study highlight the high risk of aortic death, subsequent aortic events and 341 aneurysm formation that is associated with AD/IMH/PAU diagnosis. Most importantly, even in 342 patients who survive the first 14 days after diagnosis without one of these complications, a 343 substantial aortic risk persists. This strengthens the need for further improvements in the care and 344 345 treatment of these patients, potentially advocating for more rigorous follow-up in post diagnosis aortic care and modalities of treatment for these patients. The question of how and to what extent 346 adverse aortic outcomes can be prevented most effectively remains to be the subject of further 347 research, but clearly, room exists for improvement. 348

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Tables

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

	Referents	AD/IMH/PAU	\mathbf{p}^{*}	AD/IMH/PAU Subtypes			р
	(n=399)	(n=133)		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					X		
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				S			
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 ^{\dagger}							<.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	<u> </u>	-		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 account 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 event	ts				Exclu	ding acute	events [*]	
	AD/IMH/PAU Referents AD/IMH/PAU vs. referents						AD/IMH/PAU Referents AD/IMH/PAU vs. refere					eferents
	At risk	Events	At risk	Events	HR (95% CI)	р	At risk	Events	At risk	Events	HR (95% CI)	р
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	n (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 hemator	ma (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 ul	lcer (PAU	J, 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

Fig 1. Survival free from aortic intervention for AD/IMH/PAU patients versus population
referents of similar age and gender.

5

Fig 2. Survival free from aortic rupture (a), and survival free from new aortic dissection (b) after
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**).

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Fig 4. Survival free from first time diagnosis of an abdominal aneurysm for AD/IMH/PAU patients
versus population referents of similar age and gender, including all detected aneurysms from the time
of AD/IMH/PAU diagnosis (a) and those > 14 days after diagnosis only (b).

Survival free from aortic intervention



Journe

Survival free from aortic rupture



Jonut

Survival free from new dissection



Jonut



Survival free from first time diagnosis of a thoracic aortic aneurysm

Journ



Survival free from first time diagnosis of a thoracic aortic aneurysm

Journe



Survival free from first time diagnosis of an abdominal aortic aneurysm

Jonut



Survival free from first time diagnosis of an abdominal aortic aneurysm

John