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Benefice and pitfall of direct oral anticoagulants in very high-risk myeloproliferative neoplasms

Laura Herbreteau, Loula Papageorgiou, Lenaïg Le Clech, Geoffrey Garcia, Chloé James, Brigitte Pan-Petes, Francis Couturaud, Grigorios Gerotziafas, Eric Lippert, Jean-Christophe Ianotto

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1 **Benefice and pitfall of direct oral anticoagulants in very high-risk**
2 **myeloproliferative neoplasms**

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4 **Laura Herbreteau**¹.

5 Service d'Hématologie Clinique, Institut de Cancéro-Hématologie, CHU de Brest, Brest,
6 France.

7 Email: laura.herbreteau@chu-brest.fr
8

9 **Loula Papageorgiou**^{2,3}.

10 Service d'Hématologie Biologique Hôpital Tenon, Hôpitaux Universitaires de l'Est Parisien,
11 APHP, Paris, France.

12 Research Group "Cancer, Hémostase et Angiogenèse" INSERM UMR_S 938, Centre de
13 Recherche Saint-Antoine, Faculté of Médecine, Institut Universitaire de Cancérologie,
14 Sorbonne Universités, Paris, France.

15 Email: loula.papageorgiou@aphp.fr
16

17 **Lenaïg Le Clech**^{4,9}. Service de Médecine Interne, Maladies Infectieuses et du Sang, CH de
18 Cornouaille, Quimper, France.

19 FIM, France Intergroupe des néoplasies Myéloprolifératives, France.

20 Email: l.leclech@ch-cornouaille.fr
21

22 **Geoffrey Garcia**⁵. Laboratoire d'Hématologie, CHU de Bordeaux, Bordeaux, France.

23 Email: geoffrey.garcia@chu-bordeaux.fr
24

25 **Chloé James**⁵. Laboratoire d'Hématologie, CHU de Bordeaux, Bordeaux, France.

26 Email: chloe.james@chu-bordeaux.fr
27

28 **Brigitte Pan-Petes**^{1,6}. Service d'Hématologie Clinique, Institut de Cancéro-Hématologie,
29 CHU de Brest, Brest, France.

30 INSERM, Univ Brest, CHRU de Brest, UMR 1304, GETBO, Brest, France.

31 Email: brigitte.pan-petes@chu-brest.fr
32

33 **Francis Couturaud**^{6,7}.

34 INSERM, Univ Brest, CHRU de Brest, UMR 1304, GETBO, Brest, France.

35 Département de Médecine Interne et de Pneumologie, CHRU de Brest, Brest, France.

36 Email: francis.couturaud@chu-brest.fr
37

38 **Grigorios Gerotzi**^{2,3}.

39 Service d'Hématologie Biologique Hôpital Tenon, Hôpitaux Universitaires de l'Est Parisien,
40 APHP, Paris, France.

41 Research Group "Cancer, Hémostase et Angiogenèse" INSERM UMR_S 938, Centre de
42 Recherche Saint-Antoine, Faculté of Médecine, Institut Universitaire de Cancérologie,
43 Sorbonne Universités, Paris, France.

44 Email: grigorios.gerotzi@aphp.fr
45

46 **Eric Lippert**^{8,9}.

47 Laboratoire d'Hématologie, CHRU de Brest, Brest, France.

48 FIM, France Intergroupe des néoplasies Myéloprolifératives, France.

49 Email: eric.lippert@chu-brest.fr

50 **Jean-Christophe Ianotto^{1,6,9}**.
51 Service d'Hématologie Clinique, Institut de Cancéro-Hématologie, CHU de Brest, Brest,
52 France.
53 INSERM, Univ Brest, CHRU de Brest, UMR 1304, GETBO, Brest, France.
54 FIM, France Intergroupe des néoplasies Myéloprolifératives, France.
55 Email: jean-christophe.ianotto@chu-brest.fr
56

57 **Corresponding author :**

58 Pr Jean-Christophe Ianotto
59 MD, PhD, Service d'Hématologie Clinique, Institut de Cancéro-Hématologie, Hopital Morvan,
60 CHRU de Brest, Avenue Foch, 29609 Brest cedex, France
61 Email : jean-christophe.ianotto@chu-brest.fr
62 Tel : +33298223421
63 Fax : +33298223323
64

65 **Short Title:** DOACs in very high-risk MPNs

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68

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84 **Abstract:**

85 **Introduction:** Direct oral anticoagulants (DOACs) have recently proven their efficacy and
86 safety, as primary and secondary prevention agents for thrombosis in cancer patients. We aimed
87 to determine if DOACs might be a suitable choice to reduce the thrombotic risk in
88 myeloproliferative neoplasm (MPN) patients.

89 **Materials and Methods:** We analysed a large multicentric cohort of MPN patients treated with
90 rivaroxaban or apixaban after atrial fibrillation (AF) or thrombotic events.

91 **Results:** We included 135 MPN patients with a median follow-up of 23.8 months since DOAC
92 initiation. Twenty patients (14.8%) developed 30 thrombotic events (28 arterial thromboses in
93 19 patients) for a global incidence of 6.5% patient-years. No difference was highlighted
94 between apixaban and rivaroxaban in terms of thrombosis risk, but the incidence of arterial
95 thrombosis was significantly higher on low-dose DOACs (11.9 vs. 4.5% patient-years, $p=0.04$).
96 Bleeding events were more frequent in the full-dose group (41.2 vs. 15.2%, $p=0.006$). However,
97 major and clinically relevant non major (CRNM) bleeding events occurred in 18 patients
98 (13.3%), with no difference between the groups. Age was the only identified thrombotic risk
99 factor, whereas risk factors for major or CRNM bleeding were a full-dose treatment regimen
100 and a combination of DOAC/low-dose aspirin.

101 **Conclusions:** DOACs seem effective in preventing venous thrombosis in MPN patients with
102 AF or VTE. For these high-risk patients, low-dose DOACs exposed patients to more arterial
103 thrombosis but fewer bleeding events. Prospective studies are needed to evaluate and compare
104 DOACs to the currently recommended antithrombotic drugs for high-risk MPN patients.

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108

109 **Introduction**

110 Myeloproliferative neoplasms (MPNs) are chronic haematological disorders
111 characterized by clonal proliferation of myeloid cells in bone marrow and hyperviscosity of the
112 blood due to the high concentration of these myeloid cells in peripheral blood. They induce a
113 high risk of various complications (thrombosis, haemorrhage, and phenotypical evolution).
114 Philadelphia negative (Ph-neg) MPNs include polycythemia vera (PV), essential
115 thrombocythemia (ET), pre-fibrotic myelofibrosis (PreMF) and primary myelofibrosis
116 (PMF)^[1].

117 Thrombotic and haemorrhagic events are major causes of morbidity and mortality in Ph-neg
118 MPN patients. Thrombotic risk factors have already been established : age \geq 60 years and a
119 previous history of thrombosis^[2]. Physicians should also consider cardiovascular risk factors
120 (high blood pressure, diabetes mellitus, tobacco use, obesity, and dyslipidaemia). Gender also
121 affects the incidence of venous thrombosis^[2,3]. Thromboses have been reported in 8-30% of
122 MPN patients, and more frequently in PV compared to other types of Ph-neg MPNs^[4].
123 Likewise, the *JAK2V617F* mutation increases the thrombotic risk compared to other mutations
124 (*CALR*, *MPL*) or triple-negative MPNs and it represents a strong criterion in the definition of
125 high thrombotic risk for ET patients according to the IPSET-thrombosis score^[5,6]. Arterial
126 thromboses (AT) appear to be more frequent, representing 2/3 of the events compared to venous
127 thromboembolic events (VTE), with a proportion closer to 1/2-1/2 in more recent studies^[5,7,8].
128 Atypical venous sites may be observed, such as splanchnic or cerebral vein thromboses^[9]. The
129 main risk factors identified for VTE in MPN patients are age, leukocytosis and history of
130 thrombosis^[10,11] and the recurrent VTE rate is around 6.5 per 100 pt-years in literature^[12].

131 To reduce thrombotic complications, preventive therapies are commonly prescribed in
132 addition to cytoreductive agents for high-risk patients. Low-dose aspirin is the first-choice
133 treatment in patients without a recent thrombotic history^[2,3,13]. Antiplatelet drugs are powerful

134 agents for protecting against arterial thrombosis, but they are less effective for preventing the
135 occurrence or recurrence of VTE. Vitamin K antagonists (VKA) represent an alternative and
136 can be prescribed in the long term^[14]. However, the issue is to find the right balance between
137 thrombotic and haemorrhagic risks, related to antithrombotic treatments, that are probably
138 increased by MPN. The median incidences of global bleeding and major bleeding events are up
139 to 4.6 and 0.79% patients/year, respectively, in ET and 6.5/1.05% patients/year in PV patients,
140 most frequently involving the gastrointestinal tract^[15]. The bleeding risk is particularly
141 increased in the case of extreme thrombocytosis (>1000-1500 G/L) in ET patients, due to the
142 potential occurrence of acquired von Willebrand syndrome^[3,16]. Consequently, the best agent
143 to prevent thrombotic events (AT and VTE) without increasing the bleeding incidence among
144 MPN patients remains uncertain.

145 One of the options could be prescribing oral anticoagulants (DOACs)^[17-19]. They
146 currently belong to the therapeutic quiver of prevention and treatment of VTE and a reduction
147 of AT events post atrial fibrillation (AF)^[20,21]. Furthermore, they have recently shown their
148 safety and efficacy in preventing VTE in solid cancers in several studies, such as the
149 EINSTEIN, HOKUSAI-VTE, CARAVAGGIO and SELECT-D trials^[22-26]. In these trials,
150 haematologic malignancies represented only 10% of the cancers; however, they suggested a
151 potential use of DOACs in myeloid malignancies (i.e., MPNs). DOACs have been also
152 prescribed in MPN population because of the high-risk of VTE, high incidence of AF and high
153 frequency of cardiovascular risk-factors (due to older age)^[27]. Recent studies have analysed the
154 efficacy and safety of DOACs in MPN patients^[28-32]. Their findings suggest that DOACs,
155 prescribed for AF or VTE, could prevent thrombotic events without increasing the bleeding
156 incidence in comparison with VKA, but more data are necessary to confirm the potential use of
157 DOACs in daily practice with MPN patients.

158 We have assembled a large cohort of MPN patients treated with DOACs for AF or
159 venous thrombosis. We analysed the overall thrombosis and haemorrhage rates related to
160 DOACs, and by the DOAC type (apixaban or rivaroxaban) as well as the daily dosage
161 prescribed. This multicentric retrospective study refines these findings and should help to
162 rationalize the use of DOACs in MPNs.

163

164 **Materials and Methods**

165 *Patient recruitment*

166 This trial is a French multicentric retrospective study including patients diagnosed,
167 treated, and followed up at four university or regional hospitals (Brest, Bordeaux, Quimper and
168 Tenon, Paris). MPN patients from Brest are included in the OBENE registry (Observatoire
169 Bretois des Néoplasies Myéloprolifératives, **NCT02897297**), an observational cohort of Ph-
170 neg MPN patients. MPN patients from Quimper are included in the local OFUSI registry. The
171 OBENE and OFUSI registries have been approved by the local ethics committees. All patients
172 provided written informed consent according to local procedures.

173 *Data collection*

174 All MPN diagnoses met the WHO 2008-2016 criteria^[1,33]. For each patient, we collected
175 data on demographics, mutational profile, cytoreductive agent use, the occurrence of any
176 previous thrombotic events and antithrombotic treatment. For patients with DOACs, we
177 obtained detailed information about the indications, initiation, and end-of-treatment dates and
178 about any treatment modifications. We included all MPN patients treated with DOAC, between
179 January 1st, 2012, until end of the data collection on November 1st, 2020.

180 *Analysis by subgroups*

181 Subgroups of patients were defined according to the indication for DOAC: AF (atrial
182 fibrillation), VTE (venous thrombotic event) and various (recurrent arterial events and post

183 transcatheter aortic valve implantation), by the drug used: apixaban vs. rivaroxaban and by
184 treatment intensity: full dose (rivaroxaban 20 mg once daily, OD, apixaban 5 mg *bis in die*,
185 BID) or low-dose (rivaroxaban ≤ 15 mg OD, apixaban 2.5 mg BID).

186

187 *Thrombotic and haemorrhagic events*

188 Arterial and venous (or both) thrombotic events were considered. AT included transient
189 ischaemic attack, stroke, myocardial ischaemia, intra-abdominal arterial thrombosis, and
190 peripheral arterial thrombosis (lower and upper limbs) while VTE included superficial and
191 deep-vein thrombosis in the lower and upper limbs (SVT and DVT), pulmonary embolism (PE),
192 cerebral thrombosis and intra-abdominal venous thrombosis. All included events were
193 diagnosed by the appropriate imaging techniques. Minor thrombotic events, such as
194 erythromelalgia, were not included.

195 Bleeding complications were defined according to the International Society on
196 Thrombosis and Haemostasis criteria. Thus, major bleeding was defined as fatal bleeding,
197 and/or bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular,
198 retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,
199 and/or bleeding causing a drop in the haemoglobin level ≥ 2 g/dL or more or leading to the
200 transfusion of two or more units of whole blood or red cells. Clinically relevant non major
201 (CRNM) bleeding was defined as bleeding requiring medical intervention by a health care
202 professional, and/or leading to hospitalization or an increased level of care, and/or prompting a
203 face-to-face evaluation^[34,35]. All other haemorrhages were classified as minor.

204

205 *Patient follow-up*

206 The follow-up time was defined as the time between the diagnosis and the last follow-
207 up or death. DOAC treatment time was defined as the time between the start of DOAC and the

208 definitive discontinuation of this treatment (including modifications of the DOAC or its doses)
209 or the last follow-up or death (if anticoagulation was not stopped).

210

211 *Statistical analysis*

212 Statistical analysis was performed using R[®], XLSTAT[®] and Prism GraphPad[®] software.
213 Student's and Wilcoxon's tests were used for quantitative variables, and chi-square or Fisher's
214 exact test was used for qualitative variables, with a statistical significance threshold set at p
215 <0.05. Kaplan-Meier analysis was used to perform event survival analysis and log-rank tests
216 were used to compare survival distributions between different groups, setting a threshold of p
217 value < 0.05. The rate was also calculated for thrombotic and haemorrhagic events, by dividing
218 the number of events by the total number of patient-years. Risk and predictive factors were
219 identified by constructing a Cox proportional hazards model with both univariate and
220 multivariate analyses.

221

222 **Results**

223 *Patient characteristics*

224 A total of 135 patients were included in this study (flow-chart available in **Suppl. Figure**
225 **1**). At the time of DOAC initiation, their median age was 76.7 years old, and a slight male
226 predominance (53.3%) was observed (**Table 1**). Most patients (n=125, 92.6%) presented with
227 a high risk of thrombosis according to the ELN criteria and carried at least one cardiovascular
228 risk factor (n=126, 93.3%). PV patients represented 43.7% (n=59), ET patients 38.5% (n=52),
229 primary or secondary MF patients 10.4% (n=14) and MPN unclassifiable patients 6.7% (n=9).
230 At the time of DOAC initiation or during the first three months, 105 patients (77.8%) were
231 treated with either cytoreductive drugs or phlebotomy: hydroxycarbamide was the most
232 frequently prescribed (n=73, 54.1%). Furthermore, 103 patients (76.3%) were already taking

233 low-dose aspirin (LDA) (more frequently in the low-dose DOAC group than in the full-dose
234 DOAC group) or vitamin-K antagonists alone or a combination or another anticoagulant before
235 taking DOACs.

236 A description of all thrombo-haemorrhagic events before DOAC initiation is available
237 in **Supplementary Table 1**. Thrombotic events occurred in 103 patients (76.3%), representing
238 226 events accounting for 114 arterial events in 59 (50.4%) patients, 112 venous events in 64
239 (47.4%) patients and 20 (14.8%) patients had both. Haemorrhagic events were observed in 46
240 (34.1%) patients with 44 major or CRNM bleeding events. The first and second most common
241 locations of major or CRNM bleeding events were the digestive tract (12 events, 10 patients)
242 and ear-nose-throat (ENT)(8 events, 6 patients).

243

244 *DOAC prescription*

245 DOAC treatments were started before MPN diagnosis in 35 cases (25.9%) with a median
246 time of 7 months before the diagnosis [IQR 1.7-20.2] or after MPN diagnosis in 100 cases
247 (74.1%) with a median time of 54 months [IQR 22.1-112.7].

248 The main reason for DOAC initiation was AF for 66 patients (48.9%), followed by VTE
249 in 63 patients (46.7%). Among the patients with AF, 18% received DOAC for both AF and
250 thrombotic history (6 patients had a VTE and 2 had both thrombotic events). The rest of the
251 patients received their DOAC as primary prophylaxis. Five patients started DOACs for atypical
252 or recurrent AT, and one patient started DOAC after TAVI (group “others”)(**Table 1, Suppl.**
253 **Table 1**).

254 In our cohort, apixaban and rivaroxaban were prescribed with an equal distribution (68
255 patients-50.4% of the cohort for apixaban and 67 patients-49.6% of the cohort for rivaroxaban)
256 and indications (52.9%/44.8% of each DOAC for AF and 39.7%/53.7% for VTE). A
257 predominance of curative (full) doses was observed (n=102 patients, 75.6% of the cohort). Full-

258 dose DOACs were more frequently prescribed in VTE cases than in AF situations ($p=0.001$).
259 LDA was prescribed in addition to DOACs to 17 patients (12.6%). The main reason for this
260 association was a high-risk thrombotic situation with a history of both arterial and venous
261 thrombotic events (e.g., stroke or myocardial ischemia with pulmonary embolism or deep
262 venous thrombosis).

263

264 *Thrombotic events under DOAC use*

265 During a median follow-up of 23.8 months after DOAC initiation, twenty patients
266 (14.8%) experienced at least one thrombotic event with 30 recorded events (**Table 2**). Arterial
267 thromboses were the most frequent ($n=28$ events-93.3% of the thrombotic events), mainly
268 transient ischaemic attack/stroke ($n=13$ -46.4% of the AT). The global cumulative incidence of
269 thrombosis was 6.5% patient-years (6.1 and 0.6% for arterial and venous events, respectively).

270 When comparing the apixaban and rivaroxaban groups, we did not observe any
271 significant difference in terms of thrombosis (16.2 vs. 13.4%), global cumulative incidence of
272 thrombosis (8.7 vs. 4.9% patient-years), occurrence of arterial events (16.2 vs. 11.9%) or
273 cumulative incidence of arterial thrombosis (8.7 vs. 4.3% patient-years) (**Table 2, Figures 1A**
274 **and B**). However, there was a significantly higher rate of arterial events in the low-dose group
275 than in the full-dose group (11.9 vs. 4.5%-patient-years, $p=0.04$) (**Table 2, Figures 1C and D**).

276 Patients with subsequent thrombosis were more frequent in the AF group ($n=14$ -21.2%
277 vs. $n=5$ -7.9%, $p=0.03$) with a predominance of arterial events ($n=17$ -89.5% of the thrombotic
278 events). In the VTE group, only arterial events were observed ($n=8$ in 5 patients, $p=0.05$). The
279 global and arterial cumulative incidences of thrombosis were higher in the AF group (9.6 vs.
280 3.3, $p=0.028$ and 8.8 vs. 3.3% patient-years, $p=0.048$, respectively) (**Suppl. Table 2, Figures**
281 **1E and 1F**).

282 In univariate analysis, two predictive risk factors for arterial events under DOAC
283 administration were identified: age older than 80 years at DOAC initiation and low-dose
284 DOAC, but only age >80 years-old at DOAC initiation remained significant in the multivariate
285 analysis ($p=0.03$, $HR=12.1$ [1.2;105.7])(**Suppl. Table 3**).

286

287 *Haemorrhagic events under DOAC use*

288 Forty-seven patients (34.8%) presented with at least one bleeding event, including 31
289 major or CRNM bleeding events for 18 patients (66% of the haemorrhagic events, 13% of the
290 cohort), representing global and major or CRNM bleeding incidences of 19% and 6% patient-
291 years, respectively (**Table 2**). The major/CRNM bleeding sites were mainly digestive, ENT, or
292 cerebral sites (9, 7 and 5 events, respectively).

293 No statistically significant difference was seen when comparing apixaban vs.
294 rivaroxaban in terms of the patient distribution (33.8 vs. 35.8%), major/CRNM bleeding events
295 (8.8 vs. 17.9%), or the incidence of major/CRNM bleeding events (4.7 vs. 7% patient-years)
296 (**Table 2, Figure 2A**).

297 A higher number of bleeding events was observed in the full-dose group than in the low-
298 dose group (41.2 vs. 15.2%, $p=0.006$). The global incidence was also higher (22.1 vs. 8.8%
299 patients-year, $p=0.04$) but the incidence of major/CRNM bleeding events was not (**Table 2,**
300 **Figure 2B**). Among the 17 patients treated with antithrombotic association, only 4 patients
301 (23.5%) experimented major or CRNM bleeding (urinary, digestive, cutaneous and ENT
302 localizations).

303 Between the AF and VTE groups, no statistically significant difference was observed
304 in terms of the patient distribution (33.3 vs. 38.1%), major/CRNM bleeding events (13.6 vs.
305 14.3%) or the incidence of major /CRNM bleeding events (6.3 vs. 6.2% patient-years) (**Suppl.**
306 **Table 2, Figure 2C**).

307 In multivariate analysis, we identified two risk factors that were predictive of
308 major/CRNM bleeding events: full-dose DOACs as well as DOAC and LDA combination
309 ($p=0.038$, $HR=2.18$ [1.1;69.7] and $p=0.006$, $HR=6.45$ [1.7;24.2], respectively) (**Suppl. Table**
310 **3**).

311

312 *Mortality*

313 Twenty-six patients (19.3%) in our cohort passed away during the follow-up (data not
314 shown). Major causes of death were infections, cancers, and haemorrhages. In fact, it should be
315 stressed that four patients died from a fatal bleeding (but only one patient while being under
316 DOAC treatment).

317

318 *DOAC treatment modifications*

319 For 77 patients (57% of the cohort), the DOAC treatment was modified as follows
320 (**Table 3**): the most frequent modification was temporary discontinuation in 54 patients (40%),
321 followed by a switch of DOACs type ($n=19$, 14.1%), a dose decrease (12.6%), discontinuation
322 (12.6%) or a dose increase (1.5%). Temporary discontinuations were frequent (69 events for 54
323 patients, more than 1 stop for 10 patients), mostly due to surgery or medical acts with
324 haemorrhagic risk (85% of the discontinuations). Median DOAC stop was 3 days, with only 10
325 patients (18.5%) stopping for 7 days or more, mainly due to bleedings. Changes were equally
326 frequent between the DOACs. However, it could also be observed that rivaroxaban was more
327 frequently switched to apixaban than the reverse ($n=14$, 20.9% vs. $n=5$, 7.4%, $p=0.02$), mostly
328 due to haemorrhagic complications. The dose of apixaban was more frequently reduced ($n=13$,
329 19.1% vs. $n=4$, 6%, $p=0.02$). When analysing complications occurring after DOAC
330 discontinuation, we observed 9 new thrombotic events (4 arterial and 5 venous) principally
331 during a temporary DOAC stop for a medical act with a bleeding risk. We also noticed 4

332 (major/CRNM) haemorrhagic events at the same time, mostly under LDA (**Table 4**). No
333 correlation was found between DOAC switches or dose modification and thromboembolic or
334 haemorrhagic events.

335

336 **Discussion**

337 In this study, we describe a large real-life cohort of MPN patients treated with DOACs
338 for highly prothrombotic clinical entities (mainly AF or VTE). Indeed, our patients carried a
339 very high thrombotic risk, with 92.6% of them defined as high risk by ELN criteria, 93.3% with
340 at least one cardiovascular risk-factor and 76.3% with a history of thrombosis. After a median
341 follow-up of 2 years, we highlight the fact that DOACs now belong in daily-clinical practice
342 and are clearly useful to prevent thrombotic events (mostly recurrence) in such a high-risk MPN
343 population.

344 Among these very high-risk patients, we observed a high incidence of new thrombotic
345 events under DOAC treatment with a cumulative incidence of 6.5% patient-years. This value
346 was 2.1 and 4.5% patient-years for AF and VTE patients, respectively, in a recently published
347 international cohort of MPN patients (median FU=1.7 years)^[31]. In another recent retrospective
348 study, with similar characteristics and indications to treat, the 1-year cumulative incidence of
349 thrombosis on DOAC was 5.5%^[32]. In these studies and in present one, the patients should be
350 already considered as high-risk MPNs due to the age or the presence of thrombotic events.
351 Effectively, the median age of patients at the time of DOAC prescription was 69^[31], 71^[19] and
352 77 years (present). The difference in age should be taken into account for the interpretation of
353 the comparative results (co-morbidities, co-therapies...). These results should be discussed
354 along with previous studies showing a benefit of primary prophylactic low-dose aspirin to
355 prevent thrombosis in MPNs ^[13], an incidence of thrombosis recurrence of 5.3% patient-years
356 under long-term VKA administration post-VTE ^[14] and 3.9% patient-years in long-term VKA

357 administration post splanchnic vein thrombosis^[36]. Of note, VTE recurrence occurred in 5.6%
358 of cancer patients and the 6-month cumulative VTE recurrence rate was 4% using apixaban or
359 rivaroxaban, respectively^[25,26]. Reducing the rate of thrombosis has been identified as one of
360 the unmet clinical needs for the prevention of thrombosis in MPN^[17,18].

361 Thrombotic events were slightly more frequent in the AF group (72.3%) than in the
362 VTE group (68.8%), unlike previous published cohort^[31]. Furthermore, 93.3% of events in our
363 study were arterial thromboses. From our experience thus far, patients with previous VTE never
364 experience a VTE recurrence. Thus, the percentages stress the difficulty of comparisons
365 between studies. It has been reported that arterial events are more frequent in MPN^[5,8]. Prior
366 cohorts also reported frequent arterial thrombosis in MPN patients under DOAC^[28,30,32]. One
367 possible strategy would be a combination of DOACs and aspirin. In previous publications, this
368 approach showed a decreased risk of major ischaemic events in patients with symptomatic
369 lower extremity peripheral artery disease, but it was also associated with an increased risk of
370 major bleeding^[37]. In our cohort, 12.6% of the patients received both drugs without any impact
371 on their thrombotic risk. In multivariate analysis, age (≥ 80 years old) at DOAC initiation was
372 independently associated with the thrombotic risk.

373 We also noticed a low incidence of major bleedings (2.5% patient-years) as well as a
374 low incidence of CRNM or major bleedings in our cohort (6.0% patient-years). Barbui and
375 colleagues observed an annual incidence of 2.6% patient-years of major bleeding events (3%
376 for AF patients and 2.3% for VTE patients), while How and colleagues reported in their cohort
377 a very high 1-year cumulative incidence of bleeding (12.3%, mainly major or CRNM bleeding
378 events). These results should be compared to those previously observed for MPN patients, such
379 as a major bleeding rate of 1.2% on primary prophylactic low-dose aspirin^[13]. For patients on
380 long-term VKAs, the reported incidences range from 2.0% patient-year post splanchnic vein
381 thrombosis to 2.4% post VTE^[17,36]. In a recent literature review, the median bleeding incidence,

382 after diagnosis, was evaluated at 11.5%, with the gastrointestinal tract also being the first
383 location of bleeding, as in solid cancers^[15]. These incidences were 3.8% and 6% post VTE in
384 cancer patients using apixaban or rivaroxaban, respectively^[25,26]. In multivariate analysis, a full-
385 dose treatment scheme and a DOAC/LDA association were independently associated with a
386 major or CRNM bleeding risk. The co-prescription of LDA and DOAC is low in our MPN
387 cohort. In fact, in multidisciplinary meetings when internists, cardiologists and hematologists
388 discussed about the new prescription of DOAC for a MPN patient, the frequent result is mostly
389 the change from LDA or VKA to DOAC alone. To date, there is no recommendation to co-
390 prescribe DOAC and LDA in MPN patients, mainly due to scare information and no prospective
391 trial on this subject. In front of the increased risk of bleeding with DOAC and LDA association,
392 in a population with an inherent haemorrhagic risk^[15], this association should be discussed in
393 very high-risk thrombotic situations (for instance in case of repetitive arterial event previously
394 to or under DOAC prescription), according to the risk/benefit balance.

395 An interesting point of our study was the low-dose and full-dose DOAC regimens,
396 which have never been previously investigated in MPN studies. In this very high-risk
397 population, we did not find any significant differences between the DOAC regimens in terms
398 of thrombotic events (13.4 vs. 16.2%). Nevertheless, there was a significantly higher incidence
399 of arterial events in the low-dose group (11.9 vs. 4.5% patient-years, $p=0.04$). Low-dose
400 DOACs have already been shown to prevent VTE^[38,39]. Two previous studies, the CASSINI
401 and AVERT trials^[40,41], assessed the efficacy of low-dose DOACs to prevent VTE in
402 ambulatory cancer patients. They demonstrated their efficacy in preventing VTE in comparison
403 to placebo (4.2% vs. 10.2% thrombotic events, $HR=0.41$ for apixaban^[41] and 6.0% vs. 8.8%,
404 $HR=0.66$ for rivaroxaban^[40]). On the other hand, low-dose DOACs exposed our MPN patients
405 to a lower risk of bleeding (15.2% of the patients and incidence rate at 8.8% patient-years) than
406 full-dose DOACs (41.2% and 22.1% patient-years) ($p=0.006$ and $p=0.04$, respectively). The

407 differences were not due to major or CNRM bleedings. There is currently no comparative study,
408 but the incidences of major bleeding were very low in the CASSINI and AVERT trials (2.0%
409 and 2.1%, respectively)^[40,41]. The balance of benefit/risk of this therapeutic alternative should
410 be assessed by other studies, but it seems that low-dose DOACs could be a reasonable option
411 for thrombotic prophylaxis, resulting in a low haemorrhagic risk.

412 In terms of thrombosis, we did not observe any significant difference between
413 rivaroxaban and apixaban (16.2 vs. 13.4%), the global cumulative incidence of thrombosis (8.7
414 vs. 4.9% patient-years) or arterial thrombosis (8.7 vs. 4.3% patient-years). These results are in
415 accordance with prior studies assessing rivaroxaban and apixaban in cancer-related VTE
416 treatment, which found a similar efficacy and safety of these two anti-Xa inhibitors (recurrent
417 venous thromboembolism in 5.6% of patients for apixaban, 6-month cumulative VTE
418 recurrence rate of 4% for rivaroxaban)^[25,26]. These results highlight that the two aforementioned
419 drugs can be equally prescribed, taking into account that some patients are more compliant on
420 a once-a-day treatment regimen^[42]. Barbui and How observed the same results in their cohorts,
421 but they collected data on patients treated with one out of the four DOACs, limiting the
422 possibility of identifying any such difference. They, however, found that dabigatran and
423 edoxaban were associated with a higher risk of recurrent thrombosis, as well as dabigatran was
424 more frequently associated with bleeding^[31].

425 In our cohort of very high-risk MPN patients, we observed 4/26 (15.4%) patients died
426 from haemorrhage but no one due to thrombosis. These numbers could be interpreted as a good
427 manner to choose low-dose DOAC in these situations. But the final choice should be taken
428 according to patient, comorbidities, and vascular risk. In cancer patients, it should also be
429 remembered that case fatality rates from haemorrhage or thrombosis have been calculated as
430 8.9 and 15.4%, respectively^[43].

431 Concerning the thrombotic and haemorrhagic risks, concomitant therapies could play a
432 role to reduce their incidence. Among them, cytoreductive drugs could be helpful^[44]. In our
433 cohort, we did not observe any significant difference on thrombotic and haemorrhagic incidence
434 between patients treated with or without cytoreductive drugs (data not shown).

435 In this cohort, we observed many modifications of DOAC prescriptions during the
436 follow-up (n=77, 57% of the cohort). The most frequent were transitory discontinuation (n=54,
437 40% of the patients) and switching between DOACs (n=19, 14.1%). Patients definitively
438 stopped their DOAC for 12.6% of the cohort, compared to 13.6% in a previous study^[31]. At the
439 same time, after transient or definitive DOAC discontinuation, we observed 9 new thrombotic
440 events (4 arterial and 5 venous) including 4 patients not taking any antithrombotic drug. We
441 also noticed 4 major/CRNM bleeding events, mostly under LDA. Even if we could not come
442 to any conclusion about a correlation between drug modification and complication rates, we
443 suggest that DOACs should not be stopped without multidisciplinary discussion and perhaps a
444 switch to another antithrombotic drug should be considered. This was previously highlighted
445 in MPN related splanchnic vein thrombosis, where patients after VKA discontinuation were
446 exposed to a higher thrombotic risk than those on long-term treatment (7.2 vs. 3.9% patient-
447 years)^[36].

448

449 **Conclusion**

450 We identified the retrospective design and the relatively low number of cases as possible
451 limitations of this study. However, essential information on thrombotic and haemorrhagic
452 events can be extracted from our work. A clear safety and efficiency profile of both apixaban
453 and rivaroxaban use can be observed in such a high-risk MPN population (cumulating old age,
454 AF or thrombosis history, high rate of cardiovascular risk factors...). Additional studies with
455 larger cohorts are needed to confirm DOAC as a relevant therapeutic alternative in MPN

456 patients. Furthermore, there is an important question to be addressed: could DOACs be relevant
457 as primary antithrombotic prophylaxis? In more classical MPN population, could DOACs do
458 better than the standard of care, which is aspirin?

459

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466

467 **Authorship contributions**

468 LH and JCI designed the study, analysed the data, interpreted the results, and wrote the
469 manuscript. All the authors enrolled patients. LH collected data and performed statistical
470 analysis. EL reviewed the English spelling and wrote the manuscript. FC reviewed the statistical
471 analyses. All authors critically reviewed and approved the submitted manuscript.

472

473 **Disclosure of conflicts of interest**

474 The authors declare no conflict of interest concerning this study.

475

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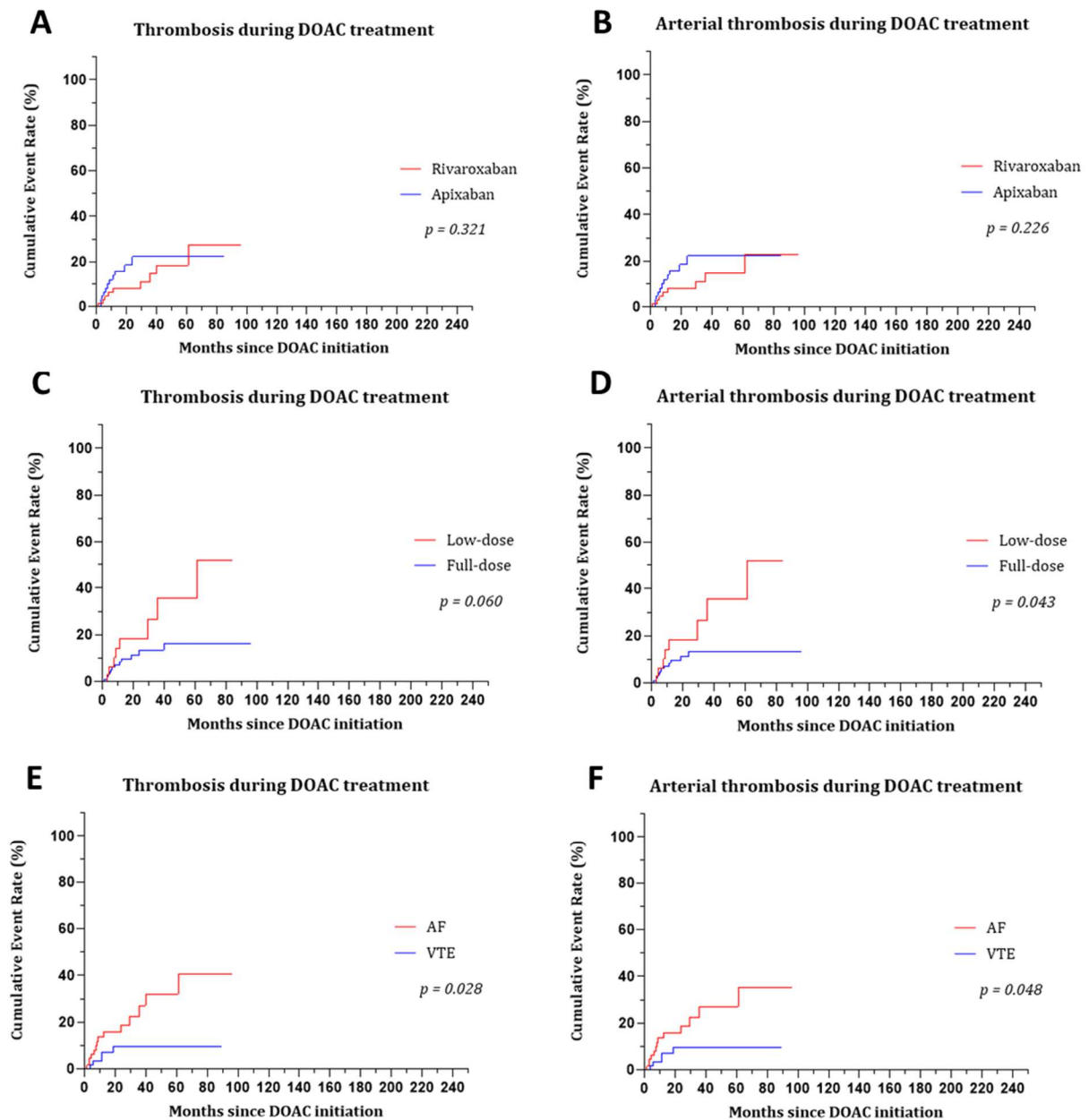
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Figures

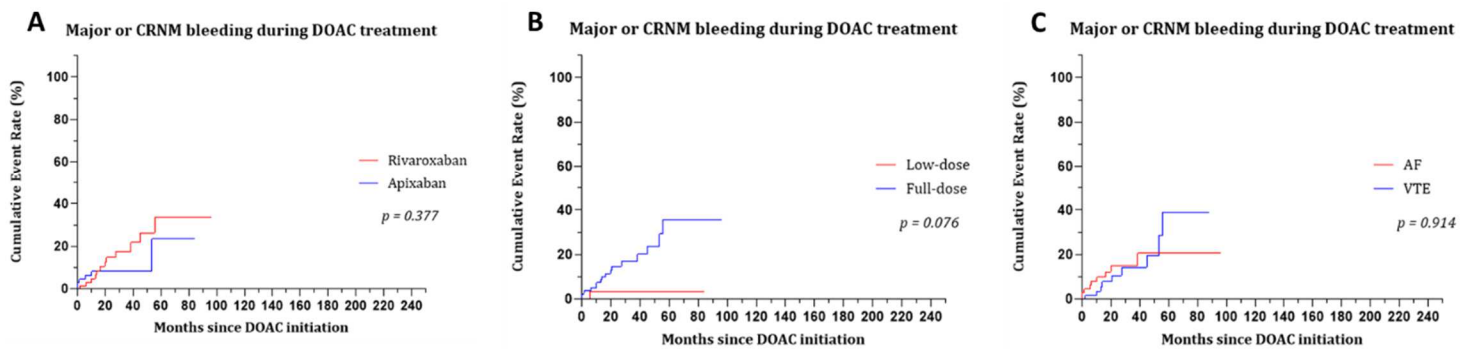
Figure 1. Kaplan-Meier curves of the thrombotic events and arterial thrombotic events in a cohort of MPN patients treated by DOACs.



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Cumulative incidence of thrombosis in rivaroxaban or apixaban groups (A), low-dose or full-dose DOAC groups (C) and atrial fibrillation or venous thromboembolism groups (E) and cumulative incidence of arterial thrombosis in rivaroxaban or apixaban groups (B), low-dose or full-dose DOAC groups (D) and atrial fibrillation or venous thromboembolism groups (F).

623 **Figure 2.** Kaplan-Meier curves of the haemorrhagic events in a cohort of MPN patients treated
624 by DOACs.
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629 *Cumulative incidence of CRNM/major bleeding in rivaroxaban or apixaban groups (A), low-*
630 *dose or full-dose DOAC groups (B) and atrial fibrillation or venous thromboembolism groups*
631 *(C).*
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Tables

Table 1. Initial characteristics of the 135 MPN patients treated with DOACs.

Characteristics at DOAC initiation	Cohort	Rivaroxaban	Apixaban	p (Rivaroxaban vs Apixaban)	Low-dose	Full-dose	p (Low vs Full-dose)
Number of patients	135	67	68	-	33	102	-
Age - median (IQR)	76.7 (69.9-83.1)	74.5 (68.2-80.7)	78.8 (71.0-84.3)	ns	82.4 (78.8-86.6)	74.3 (67.7-80.8)	<0.001
Male - no. (%)	73 (53.3)	38 (56.7)	35 (51.5)	ns	16 (48.5)	57 (55.9)	ns
Myeloproliferative neoplasms							
PV - no. (%)	59 (43.7)	31 (46.3)	28 (41.2)	ns	15 (45.5)	44 (43.1)	ns
ET - no. (%)	52 (38.5)	25 (37.3)	27 (39.7)	ns	11 (33.3)	41 (40.2)	ns
PreMF - no. (%)	1 (0.7)	1 (1.5)	0 (0)	ns	0 (0)	1 (1.0)	ns
PMF - no. (%)	4 (3.0)	2 (3.0)	2 (2.9)	ns	0 (0)	4 (3.9)	ns
Post-PV or ET MF - no. (%)	10 (7.4)	2 (3.0)	8 (11.8)	ns	6 (18.2)	4 (3.9)	0.01
MPNu - no. (%)	9 (6.7)	6 (9.0)	3 (4.4)	ns	1 (3.0)	8 (7.8)	ns
Mutation							
JAK2	117 (86.7)	59 (88.1)	58 (85.3)	ns	27 (81.8)	90 (88.2)	ns
CALR	10 (7.4)	4 (6.0)	6 (8.8)	ns	3 (9.1)	7 (6.9)	ns
MPL	3 (2.2)	1 (1.5)	2 (2.9)	ns	2 (6.1)	1 (1.0)	ns
Triple negative	5 (3.7)	3 (4.5)	2 (2.9)	ns	1 (3.0)	4 (3.9)	ns
MPN treatments							
Hydroxyurea - no. (%)	73 (54.1)	41 (61.2)	32 (47.1)	ns	20 (60.6)	53 (52.0)	ns
Pegylated interferon - no. (%)	11 (8.1)	2 (3.0)	9 (13.2)	0.03	4 (12.1)	7 (6.9)	ns
Ruxolitinib - no. (%)	6 (4.4)	3 (4.5)	3 (4.4)	ns	2 (6.1)	4 (3.9)	ns
Others - no. (%)	17 (12.6)	6 (9.0)	11 (16.2)	ns	5 (15.2)	13 (12.7)	ns
No drug - no. (%)	30 (22.2)	15 (22.4)	15 (22.1)	ns	5 (15.2)	25 (24.5)	ns
Phlebotomy - no. (%)	12 (8.9)	8 (11.9)	4 (5.9)	ns	0 (0)	12 (11.8)	0.04
High-risk of thrombosis - no. (%)	125 (92.6)	64 (95.5)	61 (89.7)	ns	30 (90.9)	95 (93.1)	ns
Cardio-vascular risk factors							
At least one - no. (%)	126 (93.3)	63 (94.0)	63 (92.6)	ns	30 (90.9)	96 (94.1)	ns
Age - no. (%)	119 (88.1)	60 (89.6)	59 (86.8)	ns	29 (87.9)	90 (88.2)	ns
High blood pressure - no. (%)	82 (60.7)	38 (56.7)	44 (64.7)	ns	23 (69.7)	59 (57.8)	ns
Hypercholesterolemia - no. (%)	46 (34.1)	23 (34.3)	23 (33.8)	ns	12 (36.4)	34 (33.3)	ns
Diabetes - no. (%)	8 (5.9)	5 (7.5)	3 (4.4)	ns	1 (3.0)	7 (6.9)	ns
Current smoking - no. (%)	11 (8.1)	5 (7.5)	6 (8.8)	ns	1 (3.0)	10 (9.8)	ns
Obesity - no. (%)	18 (13.3)	11 (16.4)	7 (10.3)	ns	4 (12.1)	14 (13.7)	ns
Complication history							
Thrombosis - no. (%)	103 (76.3)	52 (77.6)	51 (75.0)	ns	22 (66.7)	81 (79.4)	ns
Hemorrhage - no. (%)	46 (34.1)	17 (25.4)	29 (42.6)	0.03	15 (45.4)	31 (30.4)	ns
Antithrombotic drugs before DOAC initiation							
LDA - no. (%)	61 (45.2)	28 (41.8)	33 (48.5)	ns	21 (63.6)	40 (39.2)	0.01
VKA - no. (%)	27 (20.0)	12 (17.9)	15 (22.1)	ns	5 (15.2)	22 (21.6)	ns
Associations or others - no. (%)	15 (11.1)	7 (10.4)	8 (11.8)	ns	2 (6.1)	12 (11.6)	ns
No antithrombotic drug - no. (%)	32 (23.7)	20 (29.9)	12 (17.6)	ns	4 (12.1)	28 (27.5)	ns
Timing of DOAC initiation							
Before diagnosis - no. (%)	35 (25.9)	21 (31.3)	14 (20.6)	ns	3 (9.1)	32 (31.4)	0.01
After diagnosis - no. (%)	100 (74.1)	46 (68.7)	54 (79.4)	ns	30 (90.9)	70 (68.6)	0.01
Reason for DOAC initiation							
Atrial fibrillation - no. (%)	66 (48.9)	30 (44.8)	36 (52.9)	ns	25 (75.8)	41 (40.2)	<0.001
Venous thrombosis - no. (%)	63 (46.7)	36 (53.7)	27 (39.7)	ns	7 (21.2)	56 (54.9)	0.001
Arterial thrombosis - no. (%)	5 (3.7)	1 (1.5)	4 (5.9)	ns	1 (3.0)	4 (3.9)	ns
Other - no. (%)	1 (0.7)	0 (0)	1 (1.5)	ns	0 (0)	1 (1.0)	ns
LDA and DOAC association - no. (%)	17 (12.6)	4 (6.0)	13 (19.1)	0.02	5 (15.2)	12 (11.8)	ns

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DOAC: direct oral anticoagulant; ET: essential thrombocythemia; IQR: interquartile range; LDA: low-dose aspirin; NA: not applicable; no: number; ns : not significant; PMF: primary myelofibrosis; PreMF: prefibrotic myelofibrosis; PV: polycythemia vera; VKA: vitamin-K antagonists.

675 **Table 2.** Thrombotic and haemorrhagic events observed in MPN patients treated with DOACs.

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Vascular events under DOAC treatment	Cohort	Rivaroxaban	Apixaban	p (Rivaroxaban vs Apixaban)	Low-dose	Full-dose	p (Low vs Full-dose)
Number of patients	135	67	68		33	102	
Thrombotic events							
Thromboses - no. of events / no. of patients (%)	30 / 20 (14.8)	13 / 9 (13.4)	17 / 11 (16.2)	ns	10 / 8 (24.2)	20 / 12 (11.8)	ns
Incidence rate of all events (% patient-years)	6.5	4.9	8.7	ns	11.9	5.0	0.06
Incidence rate of arterial events (% patient-years)	6.1	4.3	8.7	ns	11.9	4.5	0.04
Arterial thromboses - no. of events / no. of patients (%)	28 / 19 (14.1)	12 / 8 (11.9)	16 / 11 (16.2)	ns	10 / 8 (24.2)	18 / 11 (10.8)	ns
Transient ischemic attack / stroke - no. of events / no. of patients (%)	13 / 8 (5.9)	6 / 3 (4.5)	7 / 5 (7.4)	ns	3 / 2 (6.1)	10 / 6 (5.9)	ns
Acute myocardial ischemia - no. of events / no. of patients (%)	4 / 4 (3.0)	2 / 2 (3.0)	2 / 2 (2.9)	ns	2 / 2 (6.1)	2 / 2 (2.0)	ns
Peripheral limb arterial thrombosis - no. of events / no. of patients (%)	8 / 6 (4.4)	2 / 2 (3.0)	6 / 4 (5.9)	ns	4 / 4 (12.1)	4 / 2 (2.0)	0.03
Others - no. of events / no. of patients (%)	3 / 3 (2.2)	2 / 2 (3.0)	1 / 1 (1.5)	ns	1 / 1 (3.0)	2 / 2 (2.0)	ns
Incidence rate of venous events (% patient-years)	0.6	0.5	0.7	ns	0	0.8	ns
Venous thromboembolisms - no. of events / no. of patients (%)	2 / 2 (1.5)	1 / 1 (1.5)	1 / 1 (1.5)	ns	0 / 0 (0)	2 / 2 (2.0)	ns
DVT - no. of events / no. of patients (%)	1 (0.7)	1 (1.5)	0 (0)	ns	-	1 (1.0)	ns
PE +/-DVT - no. of events / no. of patients (%)	0	0 (0)	0 (0)	-	-	0 (0)	-
Cerebral thrombosis - no. of events / no. of patients (%)	1 (0.7)	0 (0)	1 (1.5)	ns	-	1 (1.0)	ns
Patients with arterial and venous events - no.(%)	1 (0.7)	0 (0)	1 (1.5)	ns	0 (0)	1 (1.0)	ns
Haemorrhagic events							
Patients - no. (%)	47 (34.8)	24 (35.8)	23 (33.8)	ns	5 (15.2)	42 (41.2)	0.006
Incidence rate of all bleedings (% patient-years)	19.0	17.6	20.9	ns	8.8	22.1	0.04
Incidence rate of major bleedings (% patient-years)	2.5	1.6	3.8	ns	1.4	2.8	ns
Incidence rate of major and CRNM bleedings (% patient-years)	6.0	7.0	4.7	ns	1.4	7.4	ns
Major bleedings - no. of events / no. of patients (%)	16 / 8 (5.9)	8 / 3 (4.5)	8 / 5 (7.4)	ns	2 / 1 (3.0)	14 / 7 (6.9)	ns
CRNM or CRNM bleedings - no. of events / no. of patients (%)	31 / 18 (13.3)	19 / 12 (17.9)	12 / 6 (8.8)	ns	4 / 1 (3.0)	27 / 17 (16.7)	ns
Localization of major or CRNM bleedings							
Digestive - no. of events / no. of patients (%)	9 / 4 (3.0)	7 / 2 (3.0)	2 / 2 (2.9)	ns	1 / 1 (3.0)	8 / 3 (2.9)	ns
Ear-nose-throat - no. of events / no. of patients (%)	7 / 5 (3.7)	4 / 3 (4.5)	3 / 2 (2.9)	ns	2 / 1 (3.0)	5 / 4 (3.9)	ns
Cerebral - no. of events / no. of patients (%)	5 / 4 (3.0)	2 / 2 (3.0)	3 / 2 (2.9)	ns	0 / 0 (0)	5 / 4 (3.9)	ns
Muscular - no. of events / no. of patients (%)	3 / 3 (2.2)	2 / 2 (3.0)	1 / 1 (1.5)	ns	1 / 1 (3.0)	2 / 2 (2.0)	ns
Urologic - no. of events / no. of patients (%)	3 / 1 (0.7)	0 / 0 (0)	3 / 1 (1.5)	ns	0 / 0 (0)	3 / 1 (1.0)	ns
Cutaneous - no. of events / no. of patients (%)	2 / 2 (1.5)	2 / 2 (3.0)	0 / 0 (0)	ns	0 / 0 (0)	2 / 2 (2.0)	ns
Gynecologic - no. of events / no. of patients (%)	1 / 1 (0.7)	1 / 1 (1.5)	0 / 0 (0)	ns	0 / 0 (0)	1 / 1 (1.0)	ns
Others - no. of events / no. of patients (%)	1 / 1 (0.7)	1 / 1 (1.5)	0 / 0 (0)	ns	0 / 0 (0)	1 / 1 (1.0)	ns

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701 *CRNM: clinically relevant non-major; DVT: deep vein thrombosis; no: number; ns: not*
 702 *significant; PE: pulmonary embolism; VKA: vitamin-K antagonist.*

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726 **Table 3.** Modifications of DOAC administration during the follow-up of MPN patients.

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Modifications of DOAC treatment	Cohort	Rivaroxaban	Apixaban	p (Rivaroxaban vs Apixaban)	Low-dose	Full-dose	p (Low vs Full-dose)
Number of patients - no. (%)	135	67	68	-	33	102	-
At least one DOAC modification - no. of patients (%)	77 (57.0)	40 (59.7)	37 (54.4)	ns	16 (48.5)	61 (59.8)	ns
Change DOAC for another one - no. of patients (%)	19 (14.1)	14 (20.9)	5 (7.4)	0.02	4 (12.1)	15 (14.7)	ns
Hemorrhagic complication or risk - no. (%)	6 (4.4)	6 (9.0)	0 (0.0)	0.01	1 (3.0)	5 (4.9)	ns
Arterial thrombosis - no. (%)	5 (3.7)	4 (6.0)	1 (1.5)	ns	2 (6.1)	3 (2.9)	ns
Venous thrombosis - no. (%)	3 (2.2)	2 (3.0)	1 (1.5)	ns	0 (0.0)	3 (2.9)	ns
Renal failure - no. (%)	1 (0.7)	1 (1.5)	0 (0.0)	ns	0 (0.0)	1 (1.0)	ns
Other reason - no. (%)	4 (3.0)	1 (1.5)	3 (4.4)	ns	1 (3.0)	3 (2.9)	ns
Decrease of DOAC dose - no. of patients (%)	17 (12.6)	4 (6.0)	13 (19.1)	0.02	0 (0.0)	17 (16.7)	0.01
Hemorrhagic complication or risk - no. (%)	5 (3.7)	1 (1.5)	4 (5.9)	ns	-	4 (3.9)	ns
Renal failure - no. (%)	5 (3.7)	1 (1.5)	4 (5.9)	ns	-	5 (4.9)	ns
Other reason - no. (%)	7 (5.2)	2 (3.0)	5 (7.4)	ns	-	5 (4.9)	ns
Increase of DOAC dose - no. of patients (%)	2 (1.5)	0 (0.0)	2 (2.9)	ns	2 (6.1)	0 (0.0)	0.06
Arterial thrombosis - no. (%)	1 (0.7)	-	1 (1.5)	ns	1 (3.0)	-	ns
Missing data - no. (%)	1 (0.7)	-	1 (1.5)	ns	1 (3.0)	-	ns
Temporary DOAC discontinuation - no. of patients (%)	54 (40.0)	29 (43.3)	25 (36.8)	ns	14 (42.4)	40 (39.2)	ns
Surgery or medical act with a bleeding risk - no. (%)	46 (85.2)	25 (37.1)	21 (30.9)	ns	13 (19.1)	33 (32.6)	ns
Hemorrhagic complication - no. (%)	2 (3.7)	1 (1.5)	1 (1.5)	ns	0 (0)	2 (2.0)	ns
Other reason - no. of patients (%)	11 (20.4)	5 (7.5)	6 (8.8)	ns	(4.4)	8 (7.8)	ns
Definitive DOAC discontinuation - no. of patients (%)	17 (12.6)	9 (13.4)	8 (11.8)	ns	2 (6.1)	15 (14.7)	ns
Hemorrhagic complication or risk - no. (%)	5 (3.7)	3 (4.5)	2 (2.9)	ns	0 (0)	5 (4.9)	ns
Renal failure - no. (%)	2 (1.5)	1 (1.5)	1 (1.5)	ns	1 (3.0)	1 (1.0)	ns
Other reason - no. (%)	10 (7.4)	5 (7.5)	5 (7.4)	ns	1 (3.0)	9 (8.8)	ns

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746 *AF: atrial fibrillation; DOAC: direct oral anticoagulant; no: number; ns: not significant; VTE:*
 747 *venous thromboembolic event.*

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777 **Table 4.** Thrombotic and haemorrhagic events observed in MPN patients after DOAC
778 discontinuation.
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Vascular events after DOAC discontinuation	Temporary discontinuation					Definitive discontinuation				
	Cohort	Rivaroxaban	Apixaban	Low-dose	Full-dose	Cohort	Rivaroxaban	Apixaban	Low-dose	Full-dose
Number of patients - no. (%)	135	67	68	33	102	135	67	68	33	102
Thrombotic events after DOAC discontinuation										
Patients - no. (%)	9 (16.7)	4 (6.0)	8 (11.8)	1 (3.0)	8 (7.8)	1 (0.7)	1 (1.5)	1 (1.5)	0 (0)	1 (0.9)
Arterial thromboses - no. of patients (%)	4 (7.4)	1 (1.5)	3 (4.4)	1 (3.0)	3 (2.9)	1 (0.7)	1 (1.5)	0 (0)	0 (0)	1 (0.9)
Traumatic - no. of patients (%)	2 (3.7)	0 (0)	2 (2.9)	0 (0)	2 (2.0)	0 (0)	0 (0)	0 (0)	-	0 (0)
Peripheral limb arterial thrombosis - no. of patients (%)	2 (3.7)	1 (1.5)	1 (1.5)	1 (3.0)	1 (0.9)	1 (0.7)	1 (1.5)	0 (0)	-	1 (0.9)
Venous thromboembolisms - no. of patients (%)	5 (9.3)	3 (4.5)	2 (2.9)	0 (0)	5 (4.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DVP - no. of patients (%)	2 (3.7)	2 (3.0)	0 (0)	-	1 (0.9)	-	-	-	-	-
PE - no. of patients (%)	2 (3.7)	0 (1.5)	2 (2.9)	-	3 (2.9)	-	-	-	-	-
Abdominal venous thrombosis - no. of patients (%)	1 (1.9)	1 (1.5)	0 (0)	-	1 (0.9)	-	-	-	-	-
Antithrombotic drug at the time of thrombosis										
LDA - no. of patients (%)	2 (3.7)	2 (3.0)	0 (0)	0 (0)	2 (2.0)	1 (0.7)	0 (0)	1 (1.5)	-	1 (0.9)
VKA - no. of patients (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.5)	2 (3.0)	0 (0)	-	0 (0)
LWMH - no. of patients (%)	2 (3.7)	0 (0)	2 (2.9)	1 (3.0)	1 (0.9)	0 (0)	0 (0)	0 (0)	-	0 (0)
VKA + LDA - no. of patients (%)	1 (1.9)	0 (0)	1 (1.5)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	-	0 (0)
LWMH + LDA - no. of patients (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	1 (1.5)	0 (0)	-	0 (0)
No drug - no. of patients (%)	4 (7.4)	2 (3.0)	2 (2.9)	0 (0)	4 (3.9)	0 (0)	0 (0)	0 (0)	-	0 (0)
Haemorrhagic events after DOAC discontinuation										
Patients - no. (%)	4 (7.4)	2 (3.0)	2 (2.9)	1 (3.0)	3 (2.9)	5 (3.7)	3 (4.5)	2 (2.9)	1 (3.0)	5 (3.9)
Major or CRNM bleedings - no. of patients (%)	4 (7.4)	2 (3.0)	2 (2.9)	1 (3.0)	3 (2.9)	3 (2.2)	2 (3.0)	1 (1.5)	1 (3.0)	2 (2.0)
Localization of major or CRNM bleedings										
Digestive - no. of patients (%)	1 (1.9)	1 (1.5)	0 (0)	1 (3.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cerebral - no. of patients (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	1 (1.5)	0 (0)	0 (0)	1 (0.9)
Muscular - no. of patients (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	1 (1.5)	0 (0)	0 (0)	1 (0.9)
Urologic - no. of patients (%)	1 (1.9)	0 (0)	1 (1.5)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cutaneous - no. of patients (%)	1 (1.9)	1 (1.5)	0 (0)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Articular - no. of patients (%)	1 (1.9)	0 (0)	1 (1.5)	0 (0)	1 (0.9)	1 (0.7)	0 (0)	1 (1.5)	1 (3.0)	0 (0)
Antithrombotic drug at the time of bleeding										
LDA - no. of patients (%)	2 (3.7)	1 (1.5)	1 (1.5)	0 (0)	2 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Heparin - no. of patients (%)	1 (1.9)	1 (1.5)	0 (0)	1 (3.0)	0 (0)	2 (1.5)	1 (1.5)	1 (1.5)	1 (3.0)	1 (0.9)
No drug - no. of patients (%)	1 (1.9)	0 (0)	1 (1.5)	0 (0)	1 (0.9)	1 (0.7)	1 (1.5)	0 (0)	0 (0)	1 (0.9)

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797 *DOAC: direct oral anticoagulant; LDA: low-dose aspirin; LWMH: low-weight molecular*
798 *heparin; no: number.*

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