**Supplementary Material A** Variables and endpoints

<table>
<thead>
<tr>
<th>Variables</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition of venous thromboembolic event (VTE) endpoint</strong></td>
<td>VTE included all thrombosis grade ≥2 according to the Common Terminology Criteria for Adverse Events (CTCAE) classification v3.0 (56), regardless of whether the diagnosis was incidental or symptomatic. This definition excludes superficial thrombophlebitis (grade 1). The registry recorded only those thromboses that occurred during first-line chemotherapy. The reason for choosing this target was the initial intention of developing a practical predictive model for thrombotic risk in patients receiving ambulatory chemotherapy (e.g., in whom thromboprophylaxis might be useful). There were no data available for thrombosis beyond first-line chemotherapy. Diagnosis was made by means of objective imaging techniques (CT to assess antitumor response, Doppler ultrasound, etc.) depending on each center’s clinical practice. Images were not subject to control by a centralized radiology team. Thrombotic events taking place prior to initiating chemotherapy were deemed history of prior VTE and were analyzed as such separately. Successful thromboses were recorded in this registry as thrombotic recurrences.</td>
</tr>
<tr>
<td><strong>Overall survival (OS) and progression-free survival (PFS)</strong></td>
<td>OS and PFS were defined as the time between treatment initiation (first-line chemotherapy for advanced disease) and tumor progression or all-cause mortality, censoring patients lost to follow-up.</td>
</tr>
<tr>
<td><strong>Selection of variables</strong></td>
<td>To create the predictive model, we contemplated 38 clinical and histopathological covariates with a plausible relation with thrombotic risk in earlier studies. Among them are (1) patient-related factors, such as demographic data, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scale, number of chronic comorbidities according to the Charlson comorbidity index (57); laboratory parameters including platelet or leukocyte count; modified Khorana score (dichotomizing thrombocytosis at &gt; 450,000/µL) and tumor-dependent characteristics (liver tumor load, number of metastatic sites, location of metastasis, or histopathological traits).</td>
</tr>
<tr>
<td><strong>High tumor load</strong></td>
<td>High tumor load was defined as the presence ≥ 3 metastatic sites or tumor occupying ≥ 25% of the liver.</td>
</tr>
<tr>
<td><strong>Khorana risk score</strong></td>
<td>This score was applied in a modified way insofar as the AGAMENON registry considered a pre-chemotherapy platelet count &gt; 450 × 10^9/L (+1 point). The remaining variables were scored as per the model’s original description (Khorana et al, Blood 111:4902–4907, 2008): BMI ≥ 35 kg/m² (+1), prechemotherapy leukocyte count &gt; 11 × 10^9/L (+1), hemoglobin level &lt; 10 g/dL or using red blood cells growth factors (+1), gastric cancer (+2). The original description defines the high-risk group as those patients having ≥ 3 points, with a VTE rate of 6.7–7% at 2.5 months.</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td>The ECOG-PS is based on 5 grades, from 0 to 5, with 0 denoting perfect health and 5 indicating death. The purpose of this scale is to assess how the disease affects patients’ daily living abilities.</td>
</tr>
<tr>
<td><strong>Metastatic sites (organs involved)</strong></td>
<td>This variable is defined as the number of organs involved, not the number of metastases. Distant lymph node regions (cervical, thoracic, abdominal, peritoneal, retroperitoneal, inguinal, etc.) should be considered independently. The primary tumor is not counted.</td>
</tr>
<tr>
<td><strong>Signet ring cell adenocarcinoma</strong></td>
<td>This definition was considered in this study if the tumor exhibited evidence of signet ring cells, regardless of the percentage.</td>
</tr>
<tr>
<td><strong>Histological grade</strong></td>
<td>Grade denotes the degree of differentiation of cancer cells that correlates with the aggressiveness of the tumor. Pathologic grade classifies gastric cancer into 1 of 3 categories: well- (G1), moderately- (G2), or poorly-differentiated (G3).</td>
</tr>
<tr>
<td><strong>NLR ratio</strong></td>
<td>Neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the number of lymphocytes in a peripheral blood sample.</td>
</tr>
<tr>
<td><strong>HER2-positive treated tumor</strong></td>
<td>HER2-positive tumor (defined as 3+ immunohistochemical staining (IHC) or 2+ IHC with fluorescence in situ hybridization positivity) undergoing first-line trastuzumab with polychemotherapy.</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td>Major bleeding is defined as episodes in a critical location (intracranial, intraspinal, intraocular, retroperitoneal, or pericardial) associated with death; bleeding with hemoglobin levels of &gt; 2 g/dL, or bleeding requiring two units of packed red blood cells.</td>
</tr>
<tr>
<td><strong>Venous rethrombosis</strong></td>
<td>Rethrombosis was defined as a second thrombotic event after proper anticoagulant treatment of the previous event.</td>
</tr>
<tr>
<td><strong>Primary thromboprophylaxis</strong></td>
<td>In this study, primary thromboprophylaxis included those who received low molecular weight heparin for the prevention of VTE, but also those subjects who were anticoagulated for atrial fibrillation.</td>
</tr>
<tr>
<td><strong>Secondary thromboprophylaxis</strong></td>
<td>In this study, secondary thromboprophylaxis is one in which patients with paraneoplastic thrombosis initiated anticoagulant therapy before the first cycle of chemotherapy for advanced disease, and maintained it during the course of treatment.</td>
</tr>
</tbody>
</table>
Supplementary Material B

Illness-death model

State 0
"Beginning of the study"

TRANSITION #1
\(a_{01}(t)\)

"Thrombosis"

TRANSITION #2
\(a_{02}(t)\)

TRANSITION #3
\(a_{12}(t)\)

State 1
"Thrombosis"

State 2
"Tumor progression or death from any cause"

Graphical representation of survival rates over time.

Overall survival, %

No VTE
VTE within 3 months from treatment initiation
VTE 3-6 months after treatment initiation

Landmark at 6 months,
Mantel-Byar test, \(p\)-value <0.001

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>No VTE</th>
<th>VTE &lt;3 months</th>
<th>VTE 3-6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>1406</td>
<td>964</td>
<td>348</td>
</tr>
<tr>
<td>0</td>
<td>944</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>944</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>20</td>
<td>944</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>30</td>
<td>944</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>40</td>
<td>944</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>50</td>
<td>944</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>60</td>
<td>944</td>
<td>33</td>
<td>9</td>
</tr>
</tbody>
</table>
Flexible Models in Cancer-Related Thrombosis

A

B

Schoenfeld Individual Test p: 1e-04
Schoenfeld Individual Test p: 0.1145
Schoenfeld Individual Test p: 0.0567
Schoenfeld Individual Test p: 0.0786
Schoenfeld Individual Test p: 0.3936
Schoenfeld Individual Test p: 0.786
Schoenfeld Individual Test p: 0.134
Schoenfeld Individual Test p: 0.0989
Schoenfeld Individual Test p: 0.9134
Schoenfeld Individual Test p: 0.511

Global Schoenfeld Test p: 0.004294
This graph represents Kaplan-Meier's estimates of the survival function $S(t)$, for the entire population (All), for each combination of categorical covariates (e.g., yes vs no), or a single "population average" curve in the case of continuous variables (NLR, months to VTE). The time scale is from the beginning of cancer treatment. The corresponding estimates from the fitted model are overlaid (red). Abbreviations: HER2+ Human epidermal growth factor receptor 2, VTE=venous thromboembolic event, NLR=neutrophil-to-lymphocyte ratio.
```r
library(readr)
l图书馆(library)(timereg)
l图书馆(library)(flexsurv)
l图书馆(library)(Hmisc)
l图书馆(library)(mstate)

agat <- read.csv("C:/Users/Al/Desktop/agamenon/thrombosis.csv")

describe(agat)
```

```r
data:

## agat
## ## 31 Variables 2135 Observations
## ______________________________________________________
## ## ECOG
## ## n missing distinct Info Sum Mean Gmd
## 2135 0 2 0.34 278 0.1302 0.2266
## ##
## ## bone
## ## n missing distinct Info Sum Mean Gmd
## 2135 0 2 0.257 282 0.09461 0.1714
## ##
## ## cisplatin
## ## n missing distinct Info Sum Mean Gmd
## 2135 0 2 0.67 719 0.3368 0.4469
## ##
## ## burden_disease
## ## n missing distinct Info Sum Mean Gmd
## 2135 0 2 0.712 827 0.3874 0.4748
## ##
## ## Osmonths
## ## n missing distinct Info Sum Mean Gmd .05 .10
## 2135 0 973 1 12.88 11.32 1.907 2.800
## .25 .50 .75 .90 .95
## 5.293 9.666 16.225 26.032 33.916
##
## lowest: 0.0328767 0.0986301 0.1643835 0.1972602 0.2630136
## highest: 97.7095524 98.0383194 105.9287274 116.8437918 124.7341998
##
## ## pfs
## ## n missing distinct Info Sum Mean Gmd .05 .10
## 2135 0 630 1 8.101 7.516 1.184 1.874
## .25 .50 .75 .90 .95
## 3.058 5.819 9.419 15.616 21.991
##
## lowest: 0.0328767 0.0986301 0.1315068 0.1643835 0.1972602
## highest: 78.8854499 97.7095524 105.9287274 116.8437918 124.7341998
##
## ## VTE
## ## n missing distinct Info Sum Mean Gmd
## 2135 0 2 0.267 211 0.09883 0.1782
## ##
## ## Die
## ## n missing distinct Info Sum Mean Gmd
## 2135 0 2 0.428 1767 0.8276 0.2854
## ##
## ## progressive_disease
## ## n missing distinct Info Sum Mean Gmd
## 2135 0 2 0.236 1951 0.9138 0.1576
```

Thrombosis and Haemostasis
<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>missing</th>
<th>distinct</th>
<th>Info</th>
<th>Sum</th>
<th>Mean</th>
<th>Gmd</th>
</tr>
</thead>
<tbody>
<tr>
<td>cardiovascular_disease</td>
<td>2135</td>
<td>0</td>
<td>2</td>
<td>0.437</td>
<td>378</td>
<td>0.177</td>
<td>0.2915</td>
</tr>
<tr>
<td>primary_prophylaxis</td>
<td>2135</td>
<td>0</td>
<td>2</td>
<td>0.197</td>
<td>151</td>
<td>0.07873</td>
<td>0.1315</td>
</tr>
<tr>
<td>secondary_prophylaxis</td>
<td>2135</td>
<td>0</td>
<td>2</td>
<td>0.095</td>
<td>78</td>
<td>0.03279</td>
<td>0.06345</td>
</tr>
<tr>
<td>neutrophil_to_lymph_ratio</td>
<td>2135</td>
<td>0</td>
<td>2</td>
<td>.25</td>
<td>.50</td>
<td>.75</td>
<td>.90</td>
</tr>
<tr>
<td>signet_ring</td>
<td>2135</td>
<td>0</td>
<td>2</td>
<td>0.629</td>
<td>638</td>
<td>0.2988</td>
<td>0.4193</td>
</tr>
<tr>
<td>number_mets</td>
<td>2135</td>
<td>0</td>
<td>2</td>
<td>1-2</td>
<td>3</td>
<td>ó más</td>
<td></td>
</tr>
<tr>
<td>ascites</td>
<td>2135</td>
<td>0</td>
<td>2</td>
<td>No</td>
<td>Sí</td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade1</td>
<td>2135</td>
<td>0</td>
<td>2</td>
<td>Grado 1</td>
<td>Otro</td>
<td></td>
<td></td>
</tr>
<tr>
<td>trastuzumab</td>
<td>2135</td>
<td>0</td>
<td>2</td>
<td>0.394</td>
<td>332</td>
<td>0.1555</td>
<td>0.2628</td>
</tr>
<tr>
<td>Lauren_subtype</td>
<td>2135</td>
<td>0</td>
<td>2</td>
<td>Difuso</td>
<td>Intestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>days_to_VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>missing</td>
<td>distinct</td>
<td>Info</td>
<td>Mean</td>
<td>Gmd</td>
<td>.05</td>
</tr>
<tr>
<td>----------------</td>
<td>----</td>
<td>---------</td>
<td>----------</td>
<td>------</td>
<td>------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>n</td>
<td>2135</td>
<td>0</td>
<td>829</td>
<td>1</td>
<td>12.23</td>
<td>11.29</td>
<td>1.381</td>
</tr>
<tr>
<td>lowest</td>
<td>4.521</td>
<td>9.074</td>
<td>15.699</td>
<td>25.486</td>
<td>32.965</td>
<td></td>
<td></td>
</tr>
<tr>
<td>highest</td>
<td>97.76955240</td>
<td>98.03831940</td>
<td>105.92872740</td>
<td>116.84379180</td>
<td>124.73419980</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>2135</td>
<td>0</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Value</th>
<th>Anthracycline-based</th>
<th>Cisplatinlatin-based</th>
<th>Docetaxel-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>449</td>
<td>436</td>
<td>245</td>
</tr>
<tr>
<td>Proportion</td>
<td>0.210</td>
<td>0.284</td>
<td>0.115</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Value</th>
<th>Irinotecan-based</th>
<th>Other</th>
<th>Oxaliplatin-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>42</td>
<td>132</td>
<td>831</td>
</tr>
<tr>
<td>Proportion</td>
<td>0.020</td>
<td>0.062</td>
<td>0.389</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>age</th>
<th>n</th>
<th>missing</th>
<th>distinct</th>
<th>Info</th>
<th>Mean</th>
<th>Gmd</th>
<th>.05</th>
<th>.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2135</td>
<td>0</td>
<td>63</td>
<td>0.999</td>
<td>62.88</td>
<td>13.46</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>lowest</td>
<td>20</td>
<td>22</td>
<td>25</td>
<td>26</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>highest</td>
<td>84</td>
<td>85</td>
<td>86</td>
<td>88</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>surgery</th>
<th>n</th>
<th>missing</th>
<th>distinct</th>
<th>Info</th>
<th>Sum</th>
<th>Mean</th>
<th>Gmd</th>
<th>.05</th>
<th>.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALBUMIN</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burden</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tto_prev_o</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khorana</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>st</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Flexible Models in Cancer-Related Thrombosis  Carmona-Bayonas et al.

```r
## time
##  n  missing  distinct  Info  Mean  Gmd  .05  .10
## 2135      0       829       1 12.23 11.3 1.381 2.203
## .25 .50  .75  .90  .95
## lowest : 0.00328767 0.03287670 0.09863010 0.13150680 0.16438350
## highest: 97.78955240 98.03831940 105.92872740 116.84379180 124.73419900
##-----------------------------------------------------------
## khorana_score
##  n  missing  distinct  Info  Sum  Mean  Gmd
## 2135      0       2    0.683 749  0.3508 0.4557
##-----------------------------------------------------------
## cardiovascular_disease
##  n  missing  distinct  Info  Mean  Gmd
## 2135      0       2    0.391 329  0.1541 0.2608
##-----------------------------------------------------------

covs <- c("days_to_VTE"D"neutrophil_to_lymph_ratio"D"ECOG2"D"signet_ring"D"bone"D"numbe
r_mets"D"ascites"D"grade1"D"trastuzumab"D"Lauren_subtype"D"days_to_VTE","SummaryReg"D"age"D"surgery_primary_tumor"D"ALBUMIN"D"burden_disease"D"tto_prev
_o"D"cisplatin"D"khorana")

# Architecture for the multi-state model
tagatlid<-&nrow(atag)
tmat <- trans.illdeath()
tmat

## from healthy illness death
## healthy NA 1 2
## illness NA NA 3
## death NA NA NA

aga.ms <- msprep(time = c(NAD"days_to_VTE"D"OSmonths"), status = c(NAD"VTE"D"Die"), data = atag, id = "patid"Dtrans = tmat, keep = covs)

# Transition-specific covariates
aga.ms <- expand.covs(aga.ms, covs, append = TRUE, longnames = FALSE)

aga.ms$VTE_td <- 0
aga.ms$VTE_td[aga.ms$trans == %] <- &

# Parametric model selection according to AIC/BIC

data.Surv <- Surv(aga.ms$Tstart, aga.ms$Tstop, aga.ms$status)
Dist <- c("weibull"D"gengamma", "llogis"D"genf.orig"D"1norm"D"gamma")

model <- sapply(Dist, function(x) flexsurvreg(data.Surv ~ VTE_td+neutrophil_to_lymph_ratio+ascites+grade1+cisplatin+trastuzumab+I(number_mets==&burden_disease==&)+days_to_VTE.%%ALBUMIN+ECOG2+bone+signet_ring, data = aga.ms, subset = aga.ms$to==%, dist = x), USE.NAMES = T, simplify = F)
```

Thrombosis and Haemostasis
Flexible Models in Cancer-Related Thrombosis  Carmona-Bayonas et al.

AIC.model <- sapply(model, function(x) c(AIC = AIC(x), BIC = BIC(x)), simplify = TRUE)

t(AIC.model[,order(AIC.model[“AIC”, ])])

# AFT with log-logistic distribution (for survival)

f1 <- flexsurvreg(Surv(Tstart, Tstop, status) ~ VTE_td + neutrophil_to_lymph_ratio + ascites + grade1 + cisplatin + trastuzumab + I(number_mets == 1 & burden_disease == 1) + days_to_VTE.3 + ALBUMIN + ECOG2 + bone + signet_ring, data = aga.ms, subset = aga.ms$to == 3, dist = “loglogis”)

f1

# Call:
# flexsurvreg(formula = Surv(Tstart, Tstop, status) ~ VTE_td + # neutrophil_to_lymph_ratio + ascites + grade1 + cisplatin + trastuzumab + # I(number_mets == 1 | burden_disease == 1) + days_to_VTE.3 + ALBUMIN + ECOG2 + bone + signet_ring, data = aga.ms, subset = aga.ms$to == 3, dist = # “loglogis”)

# Estimates:
# data mean est L95% # shape NA 1.94713 1.87218 # scale NA 17.89058 15.01526 # VTE_td 0.08955 0.56439 -0.83539 # neutrophil_to_lymph_ratio 4.14142 0.04186 0.05206 # ascitesSI 0.24094 -0.14842 -0.24638 # grade10tro 0.90618 0.27291 0.42100 # cisplatin 0.34243 0.01598 -0.09950 # trastuzumab 0.15949 0.37484 0.26245 # I(number_mets == 1 | burden_disease == 1)TRUE 0.19403 -0.31591 -0.41975 # days_to_VTE.3 0.35836 -0.07137 -0.17380 # ALBUMINNormal 0.75949 0.11337 0.01631 # ECOG2 0.13134 -0.50179 -0.62177 # bone 0.09638 0.26414 -0.39741 # signet_ring 0.38448 0.08125 -0.17178 # U95% se exp(est) L95% # shape 2.02589 0.03990 NA NA # scale 21.18258 1.54545 NA NA # VTE_td -0.29340 0.13827 0.56871 0.43371 # neutrophil_to_lymph_ratio -0.80316 0.08520 0.09500 0.94927 # ascitesSI -0.05054 0.04994 0.86287 0.78169 # grade10tro -0.13482 0.07846 0.76116 0.66299 # cisplatin 0.06755 0.04262 0.98415 0.90529 # trastuzumab 0.48723 0.05734 1.45476 1.30012 # I(number_mets == 1 | burden_disease == 1)TRUE -0.21287 0.05298 0.72913 0.65721 # days_to_VTE.3 0.03186 0.05226 0.93111 0.84846 # ALBUMINNormal 0.23043 0.04952 1.12085 1.81645 # ECOG2 -0.38181 0.06122 0.60545 0.53699 # bone -0.13087 0.06799 0.76787 0.67206
Flexible Models in Cancer-Related Thrombosis  
Carmona-Bayonas et al.

# AFT with log-Logistic distribution (for PFS)
aga.ms2 <- msprep(time = c(NAD"days_to_VTE"D"pfs"), status = c(NAD"VTE"D"progressive_disease"),
  data = agat,
  id="patid"D
  trans = tmat,
  keep=covs)
aga.ms2$VTE_td <- 0
aga.ms2$VTE_td[aga.ms2$trans == %] <- &
aga.ms2 <- expand.covs(aga.ms2, covs, append = TRUE, longnames = FALSE)

# AFT model for PFS
f2c<-flexsurvreg(Surv(Tstart, Tstop, status) ~ VTE_td + neutrophil_to_lymph_ratio + ascites + grade1 + cisplatin + trastuzumab +
    I(number_mets == &|burden_disease == &)+ days_to_VTE.3 + ALBUMIN + ECOG2 + bone +
    signet_ring, data = aga.ms2, subset = aga.ms2$to == %, dist = "llogis")
f2

## Call:
flexsurvreg(formula = Surv(Tstart, Tstop, status) ~ VTE_td +
  neutrophil_to_lymph_ratio + ascites + grade1 + cisplatin + trastuzumab + I(number_mets ==
  1 | burden_disease == 1) + days_to_VTE.3 + ALBUMIN + ECOG2 + bone +
  signet_ring, data = aga.ms2, subset = aga.ms2$to == 3, dist = "llogis")
## Estimates:
##
data  mean  est     L95%
## shape NA 1.98182 1.90892
## scale NA 8.48197 7.19448
## VTE_td 0.07456 -0.32352 -0.70684
## neutrophil_to_lymph_ratio 4.15408 -0.83189 -0.84157
## ascitesS1 0.23927 -0.14053 -0.23462
## grade1Otro 0.90587 -0.16424 -0.29788
## cisplatin 0.34157 -0.03854 -0.11122
## trastuzumab 0.15995 0.41746 0.30944
## I(number_mets == 1 | burden_disease == 1)TRUE 0.19463 -0.26336 -0.36342
## days_to_VTE.3 0.22739 -0.35901 -0.66461

Thrombosis and Haemostasis
Flexible Models in Cancer-Related Thrombosis  Carmona-Bayonas et al.

---

```r
## ALBUMINNormal  0.75769  0.04815  0.004592
## ECOG2  0.13177  0.37288  0.49010
## bone  0.09710  -0.24540  0.37534
## signet_ring  0.30429  -0.01799  -0.10566
## shape  2.05751  0.03790  NA  NA
## scale  9.99987  0.71245  NA  NA
## VTE_td  0.05980  0.19558  0.72360  0.49320
## neutrophil_to_lymph_ratio  -0.08228  0.00494  0.96862  0.95928
## ascitesSI  -0.04645  0.04801  0.86889  0.79087
## grade10tro  -0.03069  0.06814  0.84854  0.74245
## cisplatin  0.05015  0.04117  0.96993  0.89474
## trastuzumab  0.52547  0.05511  1.51889  1.36266
## I(number_mets == 1 | burden_disease == 1)TRUE  -0.16330  0.05105  0.76846  0.69529
## days_to_VTE.3  -0.05341  0.15592  0.69837  0.51447
## ALBUMINNormal  0.14221  0.04799  1.04932  0.95512
## ECOG2  -0.25566  0.05981  0.68875  0.61257
## bone  -0.11747  0.06578  0.78161  0.68796
## signet_ring  0.06968  0.04473  0.98217  0.89973
## shape  0.895%
## scale  NA
## VTE_td  1.06163
## neutrophil_to_lymph_ratio  0.97884
## ascitesSI  0.95462
## grade10tro  0.96978
## cisplatin  1.05143
## trastuzumab  1.69125
## I(number_mets == 1 | burden_disease == 1)TRUE  0.84934
## days_to_VTE.3  0.94799
## ALBUMINNormal  1.15282
## ECOG2  0.77440
## bone  0.88917
## signet_ring  0.67216
##
## N = 2307,  Events: 1951,  Censored: 356
## Total time at risk: 17294.92
## Log-likelihood = -5829.054,  df = 14
## AIC = 11686.11

# Search of dynamic predictors
f3 <- comp.risk(Event(time, st) ~ signet_ring + ECOG2 + trastuzumab + bone +
                 cisplatin + burden_disease + trastuzumab + surgery_primary_tumor +
                 Khorana_score + cardiovascular_disease + cisplatin & cardiovascular_disease +
                 primary_prophylaxis + secondary_prophylaxis, data = agat, cause= &Dn.sim = )000Dmodel = "prop", cens.model = "cox")

summary(f3)

## Competing risks Model
##
## Test for nonparametric terms
##
## Test for non-significant terms

# (Intercept)  16.10  0.0000
## signet_ring  2.63  0.0520
## ECOG2  1.44  0.4180
## trastuzumab  1.92  0.2100
## bone  1.31  0.5480
## cisplatin  3.44  0.0028
## burden_disease  3.31  0.0076
## surgery_primary_tumor  1.27  0.6059
## Khorana_score  3.00  0.0144
## cardiovascular_disease  1.92  0.1990
## primary_prophylaxis  2.22  0.1080
```
## Flexible Models in Cancer-Related Thrombosis

Carmona-Bayonas et al.

---

```r
## secondary_prophylaxis  3.51  0.0026
## cisplatin:cardiovascular_disease  2.18  0.1280
## Test for time invariant effects
## Kolmogorov-Smirnov test p-value H_0: constant effect
## (Intercept)  3.170  0.0000
## signet_ring  0.396  0.2050
## ECOG2  0.782  0.0844
## trastuzumab  0.840  0.0574
## bone  0.529  0.2710
## cisplatin  0.704  0.0038
## burden_disease  0.562  0.0186
## surgery_primary_tumor  0.324  0.5440
## Khorana_score  0.396  0.2120
## cardiovascular_disease  1.000  0.0258
## primary_prophylaxis  1.150  0.1360
## secondary_prophylaxis  1.220  0.0036
## cisplatin:cardiovascular_disease  0.734  0.5340
## Cramer von Mises test p-value H_0: constant effect
## (Intercept)  20.200  0.0000
## signet_ring  0.310  0.1410
## ECOG2  0.226  0.4920
## trastuzumab  0.734  0.0574
## bone  0.213  0.4770
## cisplatin  0.763  0.0048
## burden_disease  0.640  0.0158
## surgery_primary_tumor  0.187  0.4920
## Khorana_score  1.180  0.0000
## cardiovascular_disease  0.417  0.4098
## primary_prophylaxis  1.810  0.3790
## secondary_prophylaxis  3.280  0.0426
## cisplatin:cardiovascular_disease  4.060  0.0674

# Flexible competing risk model

f4 <- comp.risk(Event(time, st) ~ const(signet_ring) + const(ECOG2) +
const(trastuzumab) + Khorana_score + const(primary_prophylaxis) +
secondary_prophylaxis + const(bone) + const(surgery_primary_tumor) +
burden_disease + cisplatin + const(cardiovascular_disease) +
cisplatin:const(cardiovascular_disease), data = agat, cause = &Dn.sim = )000,
model = "prop", cens.model = "cox")

summary(f4)

## Competing risks Model

## Test for nonparametric terms

## Test for non-significant effects

## Supremum-test of significance p-value H_0: B(t)=0
## (Intercept)  16.10  0.0000
## khorana_score  2.96  0.0274
## secondary_prophylaxis  4.01  0.0004
## burden_disease  3.53  0.0042
## cisplatin  2.80  0.0496
## cisplatin:const(cardiovascular_disease)  1.99  0.2310

## Test for time invariant effects

## Kolmogorov-Smirnov test
## (Intercept)  4.88
## khorana_score  2.55
## secondary_prophylaxis  1.95
## burden_disease  2.07
## cisplatin  1.92
## cisplatin:const(cardiovascular_disease)  3.07
```
Flexible Models in Cancer-Related Thrombosis  Carmona-Bayonas et al.

```r
### (Intercept)  p-value H_0:constant effect 0.0016
### Khorana_score  0.0286
### secondary_prophylaxis  0.0412
### burden_disease  0.0118
### cisplatin  0.0432
### cisplatin:const(cardiovascular_disease)  0.0238
### (Intercept)  Cramer von Mises test 21.20
### Khorana_score  1.86
### secondary_prophylaxis  6.90
### burden_disease  2.29
### cisplatin  1.77
### cisplatin:const(cardiovascular_disease)  6.40
### (Intercept)  p-value H_0:constant effect 0.0000
### Khorana_score  0.0020
### secondary_prophylaxis  0.0014
### burden_disease  0.0050
### cisplatin  0.0314
### cisplatin:const(cardiovascular_disease)  0.0644
### Did not converge, allow more iterations
### Parametric terms:
### const(signet_ring)  Coef.  SE Robust SE  z P-val lower 2.5% upper 5%
### const(ECOG)  -0.0548  0.239  0.239  -0.229  0.8190  -0.5230  0.4340
### const(trastuzumab)  0.1550  0.215  0.215  0.718  0.4720  -0.2860  0.5760
### const(primary_prophylaxis)  -0.8500  0.432  0.432  -1.970  0.0490  -1.7000  -0.0833
### const(bone)  0.1520  0.245  0.245  0.621  0.5350  -0.3280  0.6320
### const(surgery_primary_tumor)  -0.0407  0.191  0.191  -0.213  0.8310  -0.4150  0.3340
### const(cardiovascular_disease)  -0.0923  0.319  0.319  -0.289  0.7720  -0.7180  0.5330
```

#plot the results
par(mfrow=c(c(3,3)))
plot(f4, score=8)

Thrombosis and Haemostasis
```r
# Fine & Gray model, as comparison
f5 <- comp.risk(Event(time, st) ~ const(signet_ring) + const(ECOG2) +
                 const(trastuzumab) + const(Khorana_score) + const(primary_prophylaxis) +
                 const(secondary_prophylaxis) + const(bone) + const(surgery_primary_tumor) +
                 const(burden_disease) + const(cisplatin) + const(cardiovascular_disease) +
                 const(cisplatin & cardiovascular_disease), data = agat, cause = &Dn.sim = )000, model =
               "fg", cens.model = "cox")

summary(f5) #

## Competing risks Model
## Test for nonparametric terms
## Test for non-significant effects
## Supremum-test of significance p-value H_0: B(t)=0
## (Intercept) 5.26 0
## Test for time invariant effects
## Kolmogorov-Smirnov test p-value H_0:constant effect
## (Intercept) 0.0414 0
## Cramer von Mises test p-value H_0:constant effect
## (Intercept) 0.0286 0
## Parametric terms :
## Coef. SE Robust SE z P-val lower2.5% upper.5
## const(signet_ring) 0.3990 0.167 0.167 2.3800 0.0173 0.0707 0.7250
## const(ECOG2) -0.0163 0.233 0.233 -0.0703 0.9440 -0.4730 0.4400
## const(trastuzumab) 0.1920 0.211 0.211 0.9110 0.3620 -0.2220 0.6060
## const(Khorana_score) 0.3760 0.162 0.162 2.3200 0.0201 0.0585 0.6940
## const(primary_prophylaxis) -0.8910 0.442 0.442 -2.0200 0.0437 -1.7600 -0.0247
## const(secondary_prophylaxis) 0.4350 0.432 0.432 1.0100 0.3130 -0.4120 1.2800
## const(bone) 0.1810 0.243 0.243 0.7430 0.4570 -0.2950 0.6570
## const(surgery_primary_tumor) -0.0247 0.191 0.191 -0.1290 0.8970 -0.3990 0.3500
## const(burden_disease) 0.3890 0.166 0.166 2.3400 0.0193 0.0636 0.7140
## const(cisplatin) 0.3890 0.175 0.175 2.1700 0.0315 -0.0340 0.6520
## const(cardiovascular_disease) -0.0505 0.318 0.318 -0.1590 0.8740 -0.6740 0.5730
## const(cisplatin * cardiovascular_disease) 0.3170 0.456 0.456 0.6950 0.4870 -0.5770 1.2100
##
## # predictions based on flexible competing risk model vs F&G

newdata <- data.frame(signet_cells = c(1,0,1,0), ECOG2 = c(1,0,1,0),
                      trastuzumab = c(0,0,0,0), Khorana_score = c(1,0,1,0),
                      primary_prophylaxis = c(0,0,1,1), secondary_prophylaxis = c(0,0,0,0),
                      bone = c(0,0,0,0), surgery_primary_tumor = c(0,0,0,0),
                      burden_disease = c(1,0,1,0), cisplatin = c(1,0,1,0),
                      cardiovascular_disease = c(1,0,1,0))

newdata2 <- data.frame(signet_cells = c(1,0,1,0), ECOG2 = c(1,0,1,0),
                        trastuzumab = c(1,0,1,0), Khorana_score = c(1,0,1,0),
                        primary_prophylaxis = c(0,0,1,1), secondary_prophylaxis = c(0,0,0,0),
                        bone = c(1,0,1,0), surgery_primary_tumor = c(0,0,0,0),
                        burden_disease = c(1,0,1,0), cisplatin = c(1,0,1,0),
                        cardiovascular_disease = c(0,0,0,0))

a1 <- predict(f4, newdata2)
```
Supplementary Material C  Comparison of parametric models. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) are measures of goodness-of-fit. Lower values indicate a better fit.

<table>
<thead>
<tr>
<th>Model</th>
<th>AIC</th>
<th>BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-logistic</td>
<td>12174.26</td>
<td>12254.39</td>
</tr>
<tr>
<td>Generalized F</td>
<td>12175.42</td>
<td>12266.99</td>
</tr>
<tr>
<td>Generalized gamma</td>
<td>12202.47</td>
<td>12288.32</td>
</tr>
<tr>
<td>Log-normal</td>
<td>12222.72</td>
<td>12302.84</td>
</tr>
<tr>
<td>Gamma</td>
<td>12296.59</td>
<td>12376.72</td>
</tr>
<tr>
<td>Weibull</td>
<td>12366.06</td>
<td>12446.18</td>
</tr>
</tbody>
</table>

Supplementary Material D  Fine and Gray competing risk regression (for thrombotic risk)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Coefficient</th>
<th>Robust SE</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-positive treated with trastuzumab</td>
<td>0.1920</td>
<td>0.211</td>
<td>−0.2220 to 0.6060</td>
<td>0.3620</td>
</tr>
<tr>
<td>Tumor with signet ring cells</td>
<td>0.3980</td>
<td>0.167</td>
<td>0.0707 to 0.7250</td>
<td>0.0173</td>
</tr>
<tr>
<td>ECOG-PS, ≥ 2</td>
<td>−0.0163</td>
<td>0.233</td>
<td>−0.4730 to 0.4400</td>
<td>0.9440</td>
</tr>
<tr>
<td>Khorana score, ≥ 3 Ψ</td>
<td>0.3760</td>
<td>0.162</td>
<td>0.0585 to 0.6940</td>
<td>0.0201</td>
</tr>
<tr>
<td>Surgery on primary tumor (baseline)</td>
<td>−0.0247</td>
<td>0.191</td>
<td>−0.3990 to 0.3500</td>
<td>0.8970</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>0.1810</td>
<td>0.243</td>
<td>−0.2950 to 0.6570</td>
<td>0.4570</td>
</tr>
<tr>
<td>Use of anticoagulant therapy ‡</td>
<td>−0.8910</td>
<td>0.442</td>
<td>−1.7600 to −0.0247</td>
<td>0.0437</td>
</tr>
<tr>
<td>Primary prophylaxis</td>
<td>0.4350</td>
<td>0.432</td>
<td>−0.4120 to 1.2800</td>
<td>0.3130</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High tumor load §</td>
<td>0.3890</td>
<td>0.166</td>
<td>0.0636 to 0.7140</td>
<td>0.0193</td>
</tr>
<tr>
<td>Cisplatin-containing regimen</td>
<td>0.3090</td>
<td>0.175</td>
<td>−0.0340 to 0.6520</td>
<td>0.0775</td>
</tr>
<tr>
<td>≥ 60 years of age, with chronic cardiovascular disease §</td>
<td>−0.0505</td>
<td>0.318</td>
<td>−0.6740 to 0.5730</td>
<td>0.8740</td>
</tr>
<tr>
<td>Cisplatin-containing regimen (interaction)</td>
<td>0.3170</td>
<td>0.456</td>
<td>−0.5770 to 1.2100</td>
<td>0.4870</td>
</tr>
</tbody>
</table>

‡The Khorana score was evaluated in a modified way since the registry considers the pre-chemotherapy platelet count ≥450 × 10⁹/L.

Primary thromboprophylaxis included those subjects who received low molecular weight heparin for the prevention of cancer-associated thrombosis, but also subjects anticoagulated by atrial fibrillation. Secondary thromboprophylaxis included those individuals anticoagulated by paraneoplastic thrombosis prior to either first-line chemotherapy or diagnosis.

Chronic cardiovascular disease includes chronic heart disease, peripheral vascular disease, and previous cerebrovascular disease.