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Clinical outcomes under hydroxyurea treatment in polycythemia vera: a systematic review and meta-analysis.

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Abstract

Hydroxyurea is the standard treatment in high risk patients with polycythemia vera. Yet, estimates of its effect in terms of clinical outcomes (thrombosis, bleeding, hematological transformations and mortality) are lacking. We performed a meta-analysis to determine the absolute risk of events in contemporary patients under hydroxyurea treatment.

We searched for relevant articles or abstracts in the following databases: Medline, EMBASE, clinicaltrials.gov, WHO International Clinical Trials Registry, LILACS.

Sixteen studies published from 2008 to 2018 reporting number of events using WHO diagnosis for polycythemia vera were selected. Through a random effect logistic model, incidences, study heterogeneity and confounder effects were estimated for each outcome at different follow-ups.

Overall, 3,236 patients were analyzed. While incidences of thrombosis and acute myeloid leukemia were stable over time, mortality and myelofibrosis varied depending on follow-up duration.

Thrombosis rates were 1.9, 3.6 and 6.8% persons/year at median ages 60, 70 and 80 respectively. Higher incidence of arterial events was predicted by previous cardiovascular complication. Leukemic transformation incidence was 0.4% persons/year. Incidence of transformation to myelofibrosis and mortality were significantly dependent on age and follow-up duration. For myelofibrosis, rates were 5.0 at 5 year and 33.7% at 10 years; overall mortality was 12.6% and 56.2% at 5 and 10 years respectively.

In conclusion, we provide reliable risk estimates for the main outcomes in polycythemia vera patients under hydroxyurea treatment. These findings can help design comparative clinical trials with new cytoreductive drugs and prove the feasibility of using hard endpoints for efficacy, such as major thrombosis.

Introduction

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by clonal proliferation of the erythroid, myeloid, and megakaryocyte lineages. This disease is recognized for its distinct molecular profile (JAKV617F mutation) and has a characteristic natural history marked by high frequency of thrombosis and a tendency to transform into acute myelogenous leukemia (AML) or myelofibrosis (MF). The first step in approaching an individual patient with PV is to identify the potential risk of developing major thrombotic or hemorrhagic complications. In patients younger than 60 years carrying only reversible or controllable

cardiovascular risk factors, and without prior history of thrombosis, phlebotomy (PHL) and low dose aspirin are recommended. Cytoreductive therapy with either hydroxyurea (HU), a ribonucleotide reductase inhibitor considered non mutagenic, or Interferon-alfa (IFN) are appropriate first line drugs to prevent vascular complications in high risk patients (age >60 y and/or prior thrombosis)¹.

HU was recommended in the treatment of high risk PV based on the results of PVSG protocol 08 in which this drug was found to be effective in reducing the rate of thrombotic events in 51 patients compared to an historical controls treated with PHL alone². Very few studies were designed to confirm these conclusions. Recently, a propensity score analysis of patients enrolled in the ECLAP trial documented superiority of HU in reducing thrombosis compared with well-matched control patients treated with PHL only³. In three recent randomized controlled trials (RCT) in PV⁴⁻⁶, HU was compared to IFN; unfortunately, primary end-point was not the reduction of vascular complications but included only hematological response, that cannot be considered a surrogate of vascular events⁷. The only demonstration of an antithrombotic efficacy results from 2 RCT in essential thrombocythemia (ET) in which the drug was superior to chemotherapy-free and to anagrelide control arms^{8,9}. Hence, the lack of solid demonstration of thrombosis prevention or survival advantage in PV and the concern that HU may increase the risk of leukemia led to an underuse of this drug in clinical practice¹⁰ and to suggest that the first line cytoreductive therapy in PV should be PHL only, irrespective of patient risk category¹¹.

However, even in the absence of clear demonstration of benefit, there is a consensus among ELN and NCCN experts of HU use in high risk cases and the drug is currently the first-line therapy in clinical practice. We have now several observational studies reporting single or multicenter experience regarding the risk-estimates of clinical events associated with HU so that we deemed useful to provide a summary of these results in order to help clinical decision making and to offer estimates for a more realistic sample calculation in future comparative clinical trials. To answer this unmet knowledge need a great effort of data retrieval and analysis is necessary. Based on these premises, we carried out a literature review aimed at systematically assess and meta-analyze the incidence rate and absolute risk of events in patients treated with HU.

Methods

Inclusion criteria

The protocol of the original review was registered in PROSPERO (number CRD42018117814¹²).

Inclusion criteria were:

- 1) Studies in English published in the last ten years (2008-2018) using WHO diagnostic criteria for PV.
- 2) Studies on adult (aged ≥ 18) non-pregnant patients.
- 3) Randomized Clinical Trials (RCTs), prospective and retrospective cohort studies reporting frequency of outcomes of interests (thrombotic and/or hemorrhagic events and/or hematological transformations in adult patients) stratified by Hydroxyurea therapy, as reported by authors.
- 4) Studies with at least 20 participants.

The following studies were excluded: case reports, cross-sectional studies, editorials, and narrative reviews. Studies aimed specifically at HU resistant patients were excluded.

In case of duplicate studies on the same sample, the most numerous, or most informative, or most recent study was taken into consideration. Studies not reporting follow-up duration were excluded.

Search strategy

We searched for articles or abstracts published between 2008 and 2018 in the following database: Medline, EMBASE, clinicaltrials.gov, WHO International Clinical Trials Registry (for unpublished or ongoing trials), LILACS.

Terms used in research for primary endpoints were *polycythemia vera*, *hydroxyurea/hydroxycarbamide*, *thrombosis*, *myelofibrosis*. Research was focused on primary outcomes, although we also collected data on secondary outcomes (survival, leukemia, bleeding). Whenever possible, specific filters were used to exclude case reports, reviews, animal studies and studies on very young patients (aged < 18) or pregnant women.

Conference abstracts and posters reporting relevant data were not excluded from consideration. Duplicate records were individually checked and merged using reference managing software.

Data extraction

The following data were extracted from selected studies:

Type of study, mean (or median) follow-up duration, number of HU treated patients in the study, incidence of myelofibrotic and/or leukemic transformations, number of patients with at least 1 incident or recurrent episode of thrombosis or 1 bleeding, mortality, median/mean age, gender of patients, number of patients with cardiovascular risk factors, number of patients with history of thrombosis, number of patients undergoing antiplatelet or anticoagulant therapy. Whenever possible, number of patients with major arterial or venous thrombosis was extracted as well.

Quality assessment

Quality assessment of eligible studies was performed independently by two reviewers (T.B. and A.F.) according to the Joanna Briggs Institute Critical appraisal tool for studies reporting prevalence data¹³. The tool evaluates methodological quality of studies according to a 9-objects scale accounting for representativeness of the sample, accuracy of reporting, adequacy of diagnostic criteria and statistical analysis.

Statistical analysis

Incidence of each outcome was calculated and is reported as number of event per 100 persons/year. Forest plots show punctual estimates with exact binomial 95% confidence intervals for each study and globally. Persons/year were estimated by multiplying mean follow-up duration by number of HU treated patients; when mean follow-up duration was not available, median duration was deemed to be a reasonable approximation.

In order to obtain global adjusted incidence estimates a logistic Generalized Linear Mixed Model (GLMM) was used for meta-regression of outcomes on study-specific confounders. The model included follow-up duration and known risk factors for the outcome as fixed effects; the random component of the model included a random slope for follow-up duration in studies. The method assumes that probability of displaying the event at time zero is the same across the studies, but it increases as a function of follow-up duration at a study-specific rate under the effect of selected covariates. The advantage of this model is that it uses an exact binomial likelihood and error structure and naturally accounts for heterogeneity in sample sizes¹⁴⁻¹⁶. For meta-regression, missing data about confounders were imputed to the sample size-weighted mean of the other studies. For reasons of interpretability and estimability of the model, predictor variables were all centered on their weighted mean. Intraclass Correlation Coefficients (ICC) were calculated conditional on fixed effects = 0 (i.e. the mean) and reported as heterogeneity measure.

To evaluate whether results could depend on model choice, a sensitivity analysis was conducted by fitting a negative-binomial regression on events count, with persons/year as exposure variable. As opposed to the GLMM, such a model assigns the same weight to each study regardless of sample size and assumes a constant yearly event rate with no upper bound.

Results

Literature search and study characteristics

The study selection process is detailed in Fig. 1.

The search on Medline and EMBASE retrieved a total 420 results; 9 additional results were retrieved from different sources (clinicaltrials.gov, Cochrane Central Register of Controlled Trials, WHO International Clinical Trials Registry, references from relevant articles) for a total 429 results, which were reduced to 340 after duplicates removal. Abstract and full-text screening allowed for the exclusion of 291 articles, as they fell into the following categories: reviews, case reports, animal studies, patients aged less than 18 or in pregnancy. Other studies were not considered as they had a total sample size of less than 20 patients, and/or they did not report incidence data or follow-up duration.

Consequently, a total 49 studies were selected for methodological evaluation. 33 were excluded for the following reasons: 11 had unclear reporting of data (e.g. it was impossible to distinguish data due to HU-treated patients from those due to other cytoreductive treatments, or PV from other myeloproliferative neoplasms); 7 did not meet the number of 20 HU treated patients as required by our study protocol; 7 studies referred to cases diagnosed outside the time window (2008-2018) and not with WHO 2008-2016 criteria; 1 missed follow-up data, 1 was specifically aimed at HU resistant patients. In case of multiple studies from the same author(s), we inquired whether they referred to overlapping populations, by questioning authors when necessary, and excluded duplicates (6 studies) from review. The final selection comprised 14 full text articles and 2 conference abstracts to be included in the meta-analysis.

Table 1 summarizes the main characteristics of the 16 eligible articles and abstracts. The selection included 3 reports on 2 RCTs^{4,17,18} (one comparing HU and Interferon therapy and one HU to Ruxolitinib), 1 RCT where HU was not a comparator¹⁹ and 12 observational retrospective cohort studies^{7,20,29-33,21-28}. The great majority of the studies were conducted in Europe and some involved multiple countries; only one study in our selection³² was conducted in the US.

Number of HU treated patients ranged from 25 to 890 across studies; the final meta-analysis was conducted on a total of 3,236 patients in whom HU therapy was consistently administered. Follow-up duration ranged from 0.3 to 12.4 years.

Quality of studies was judged using the JBI critical appraisal tool for prevalence studies considering sample size, representativeness of the sample, sampling methods, objectively measured outcomes, and adequate information on follow-up duration and potential confounders.

Only two studies in our review, both by Alvarez-Larrán et al.^{7,21}, were specifically aimed at obtaining incidence estimates under HU treatment, and thus fully met these criteria. The other studies, not addressing the same specific question about outcomes of HU treatment, often missed some of the above information; the most frequent issue was lack of stratification by HU treatment. For 6 of these studies, we readily had access to original databases, allowing us to fully extract data about HU treatment, outcomes and potential confounders. We were unable to retrieve full information from 2 additional reports^{4,29}, but we could extract incidence of at least one of the outcomes of interest regardless. In 8 studies we were able to univocally distinguish arterial and thrombotic events in 2,048 patients^{7,19,23,26-28,31,33}.

Overall, demographics were incomplete or not stratified by HU treatment (6 studies); cardiovascular risk factors were missing (10 studies), and history of thrombosis was not reported (6 studies); antithrombotic drug therapy was not mentioned in 10 studies. However, in spite of missing data, in each of these studies we could retrieve the number of events for at least one outcome.

Two studies referred to the same population^{4,17}, but reported different outcomes, therefore we did not consider it as a duplicate for the aims of our analysis.

While most studies pertained to events after first line therapy, 3 focused on recurrent thromboses.

HU and risk of outcomes

Summary of events

Figure 2 shows forest plots of the study-specific and pooled yearly incidence of each outcome of interest as % person/years with 95% binomial CI.

The incidence of outcomes shows remarkable variability across studies. In particular, with the exception of AML, for the other outcomes 95% confidence intervals do not always overlap between studies.

A mixed effect logistic model was applied to the data in order to obtain incidence estimates adjusted for heterogeneity and study-specific confounders, including follow-up duration. Confounding effects that were controlled for in meta-regression were age (for all outcomes), percent of patients under antiplatelet/anticoagulant therapy (for mortality and thrombosis), percent of patients with history of thrombosis (mortality, thrombosis), percent of patients with cardiovascular risk factors (mortality, thrombosis). Overall, regression analysis of MF and AML was only adjusted for age. Results from logistic regression are detailed in Supplementary Table 1. Diagnostics of model fit were performed by visual inspection of observed vs. fitted plots (Supplementary Figure 1).

Fig. 3 shows probability of each outcome in follow-up as predicted by regression models when all confounders are kept fixed at their weighted mean value, with estimated ICC and relative statistical tests of heterogeneity. Since all predictor variables were centered on the mean, predictions are to be interpreted as incidence in the presence of confounding factors equal to the (weighted) mean.

Event heterogeneity and timing

No evidence of excess heterogeneity was found in meta-regression for MF ($P=0.281$) and AML ($P=1.000$) once adjusted for potential confounders, as opposed to mortality and thrombosis, where a small but non-zero amount of heterogeneity was observed despite adjustment. The distribution of events during follow-up as carried out by meta-regression highlighted a significant effect of age on probability of MF and thrombosis (and obviously on mortality), but not of AML (Fig. 2 and Suppl. Table 1). This effect is particularly strong for thrombosis. Remarkably, history of thrombosis was not a significant predictor of thrombosis risk in meta-regression.

A logistic model allows for incidence rates to change over time. To confirm that our results do not heavily depend on this assumption, we carried out a sensitivity analysis comparing the logistic GLMM to a negative binomial regression. In a negative binomial regression, yearly incidence is assumed constant over time. Results from the two models were fundamentally in agreement for thrombosis and AML outcomes, whereas for MF and overall mortality they started diverging after 5-years of follow-up. This indicates that, for practical purposes, thrombosis incidence rate can be assumed to be constant over time, at least up to a 10-years observation period.

Thrombosis incidence

Adjusted estimates for annual incidence of thrombosis are reported in Table 2, globally and stratified by median age and previous thrombosis. Average incidence rate was 3.3% persons/year, ranging from 1.9% at 60 years with no history of thrombosis to 6.8% at a median age of 80 years. Estimates increase with median age and are higher in presence of history of thrombosis, but the latter difference is not statistically significant. On the other hand, in a sub-analysis on arterial and venous thrombotic events, previous thrombosis was a highly significant ($P<0.001$) predictor of incidence of arterial thrombosis, but not of venous.

Hematological transformations and mortality

Of note, incidence of MF and overall mortality increases steeply after 5 years of follow-up according to the logistic GLMM. Estimates of myelofibrosis risk at a median age of 68 years are 0.9%, 5.0% and 33.7% at 1, 5 and 10 years respectively, whereas mortality under the same conditions was 2.4%, 12.6% and 56.2%, but these estimates increase or decrease with age at the start of follow-up. Specifically, the odds of MF transformation increase on average 6% (95% CI 1-11%) for each year of age, while those of mortality increase by 21% (95% CI 9-33%).

AML evolution, on the other hand, showed a stable incidence over time. According to the negative binomial model the annual rate of AML transformation was 0.4%, although the logistic model suggests a slight tendency to increase after about 8 years.

Bleeding

The number of major bleedings was deemed too small for reliable inference. Based on 88 events over 1,485 patients, bleeding pooled incidence was 1% per year, independently of follow-up duration and antithrombotic therapy, as shown by meta-regression. This estimate was quite consistent, since no evidence of study heterogeneity was found for this outcome, but the small sample size may limit accurate detection of these effects.

Second cancer and side effects

The number of second cancers was too small, and between-study heterogeneity too high to allow for reliable inference on this outcome. Based on 59 events on 755 patients, pooled incidence of second cancer was 1.7% persons/year (95% CI 1.3-2.2%), mainly comprising non-melanoma skin cancer.

Only two studies in our selection reported HU-associated adverse events, which does not allow to produce reliable estimates.

Discussion

(i) Summary of results

We systematically collected literature on the benefit-risk profile of HU treatment in patients diagnosed with PV published in the 2008-2018 period. Out of 429 records, we selected 16 reports which allowed retrieval of incidence of specific clinical outcomes in these patients: namely major thrombosis, bleeding, evolution into MF and/or AML, mortality.

Thrombosis

In previous studies the incidence of thrombosis in high-risk PV patients candidates to cytoreductive treatment has been estimated from large patient cohorts including either patients under HU and patients not receiving cytoreduction or taking drugs other than HU^{34,35}, so that the effect of HU was not clearly evidenced. Overall thrombosis incidence in our population was about 3% per year, obtained by pooling together event rates from each study. This estimate does not account for heterogeneity across studies, yet a meta-regression analysis accounting for study-specific confounders such as median age, antithrombotic therapy, CV risk factors and history of thrombosis provides a slightly lower estimate of 2.8%. This rate does not seem to change over follow-up time, as shown by a comparison between a logistic and a negative binomial model, and depends on age. Based on 2,552 patients and 469 events, estimates of thrombosis incidence rate, in patients with a median age of 60, 70 and 80 years under HU treatment are 1.6%, 3.6% and 6.8% respectively.

Contrary to what is widely known, we did not find a statistically significant effect of history of thrombosis on incidence of new vascular events. Yet, this is not surprising in meta-regression analysis, since it is prone to the “ecological bias”, i.e. the loss of information that follows from dealing with aggregate data³⁶.

This mirrors the effect of increasing age on the thrombotic risk of the general population observed either for arterial and thrombotic events^{37,38}; however, we highlight that the residual incidence of thrombosis in HU treated PV patients is still elevated, corresponding to approximately 10-fold higher than the one estimated in the general population³⁷. It is therefore advised to promote new pharmacological strategies and to consider our reported thrombosis rate as a benchmark for future comparative studies.

Hematological transformations, mortality and second cancer

In regard to hematological transformations, we observed that AML annual incidence is fairly constant and the cumulative 10-year incidence is about 4% (0.4% patients/year).

In contrast, annual incidence of evolution into MF, as predicted by meta-regression, increases steeply after 5

years of follow-up. Therefore, in the 0-5/5-10 years of observation periods the average annual rate of MF evolution was 1.0% and 5.7% respectively.

Mortality followed a similar pattern as MF, although divergence of the two meta-regression models was much less remarkable, with 95% CI overlapping.

The incidence of second cancer we retrieved was 1.7% patients per year. However, the reliability of this estimate is dubious because of the limited number of events and the very large between-study heterogeneity for this outcome.

(ii) Strengths and limitations

The first major strength of our work is the remarkable sample size we were able to achieve, which allowed us to obtain robust estimates for the most relevant outcomes in PV.

However, a possible limitation of our analysis is that most reports did not specifically address our study questions, and consequently the relative estimates are based on raw frequency data extracted from descriptive tables or text. Furthermore, we cannot exclude bias in reporting events in individual studies, since most of these were not specifically designed to answer our primary questions. On the other hand, the fact that the studies did not address our question makes publication bias in favor of certain results very unlikely.

A second strength of our approach is that we managed to greatly reduce the issue of study heterogeneity by using adequate statistical methods, namely a logistic GLMM. In this way we mitigated the distortion due to this factor. Furthermore, by adjusting for study-specific covariates, we were able to account for the effect of the most relevant confounders, which for some outcomes (namely MF and AML) allowed us to reduce heterogeneity to negligible values. Of note, for most studies we were able to extract data on study-specific confounders stratified by treatment; this is expected to greatly reduce the effect of “ecologic bias, which is a common issue in meta-analysis of aggregated data. A limitation is that while our methods supposedly reduce ecological bias, it is likely impossible to entirely remove its effect in a meta-regression on aggregate data. Some known predictors of clinical outcomes, such as history of thrombosis, which is a well-known risk factor for recurrences, turned out to be not-significant in meta-regression. This may suggest that under HU treatment history of thrombosis is not a risk factor for recurrences anymore; but it may also be a byproduct of using aggregate data as predictors, with subsequent loss of information on individual patients³⁶.

A third strength is that by extracting data on follow-up duration and integrating them in the analysis we were able to model the time dependent evolution of outcome risk, thus overcoming a common bias in meta-analysis of binary outcomes that is lack of temporal information. A potential source of bias in this respect is our choice to use median follow-up time when mean was not available, which can lead to biased risk estimates when the actual distribution of follow-up times in the study is very skewed. Yet, using the median as an estimator of mean has been shown to be reliable in most cases³⁹.

(iii) Conclusions

This meta-analysis provides reliable risk estimates for thrombosis, hemorrhage, evolution to MF and AML, and mortality in PV patients under standard treatment with HU. This can be a valid reference for clinician, it can support patient communication and counseling, and also constitutes a help for sample size calculations in future comparative clinical trials by providing a reference value. We also prove the feasibility of clinical trials adopting hard efficacy endpoints such as frequency of cardiovascular events in selected populations. Lastly, we underline the value of an old, cheap, and safe molecule as a reliable and accessible resource for those settings where there is need to reconcile economic sustainability with the right to a quali-quantitative life advantage.

Conflict of interest

The authors declare no conflict of interest.

Authors contribution

Tiziano Barbui conceived the research and wrote the manuscript; Alberto Ferrari performed the analysis and wrote the paper; Alessandra Carobbio, Arianna Masciulli, Arianna Ghirardi, Guido Finazzi, Valerio De Stefano and Alessandro Maria Vannucchi reviewed and approved the paper.

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Table 1: summary of study characteristics

Study	N	FUP years	Median age (range)	Sex (M/F)	Mortality	MF	AML	Thrombosis	Bleeding	Study quality ²
Alvarez-Larrán, A. et al.(2012)	261	7.2	64 (16-88)	118/143	48	20	8	45	23	9/9
Alvarez-Larrán, A., Kerguelen, A., et al.(2016)	890	4.6	68 (18-95)	452/438	99	39	17	71	48	9/9
Barbui, T. et al.(2014)	137	7.7	60.5 (23-83)	69/68	16	12	3	21		8/9
Bonicelli, G. et al.(2013)	114	11					7			6/9
Crisa, E. et al.(2017)	35	6.3	55 (36-65)	23/12	3	3	2	3		8/9
De Stefano, V. et al. (1)(2016)	34	5.1	51.5 (19-80)	10/24	3	2	1	10	5	8/9
De Stefano, V. et al. (2)(2016)	45	7	71.5 (46-90)	24 / 21	3	6	1	7	1	8/9
De Stefano, V. et al.(2018)	104	3.7	73 (43-95)	46/58	16	2	2	18		8/9
Gisslinger, H. et al.(2016)	127	1	60 (21-81)	60/67	0	0	0	2		5/8 (1)
Gisslinger, H. et al.(2017)	73	2.7			0	0	2			5/8 (1)
Hintermair, S. et al.(2018)	25	8						7	2	8/9
Lussana, F. et al.(2014)	46	12.4	35.8 (22-40)	22/24	3	6	1	19	6	8/9
Marchioli, R. et al.(2013)	184	2.4	71 (44-87)	108/76	6	3	1	16	3	8/9
Mesa, R. et al.(2017)	56	0.3	66 (19-85)	34/22	1	0	0	2		6/7 (2)
Podoltsev, N. A. et al.(2018)	497	2.83	77		173			118		8/9
Tefferi, A. et al.(2013)	608	6.9	63.3 (19-95)	296/312	151	64	18	130		8/9
Total	3,236	.	68.4¹		522/3,097	157/2,600	63/2,714	469/2,552	88/1,485	

¹Weighted mean² Evaluation on 9 items according to JBI appraisal tool for prevalence studies. In parenthesis number of items for which evaluation was not applicable based on study design.

Table 2: Thrombosis incidence by age and history of thrombosis

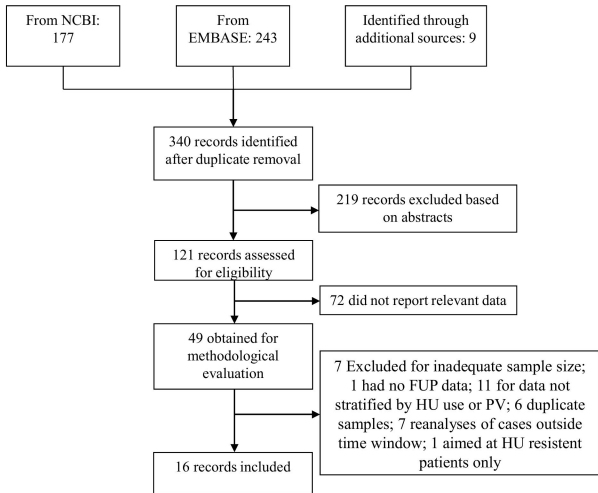
	Age											
	Average			60 years			70 years			80 years		
	<i>Risk</i>	<i>95% CI</i>		<i>Risk</i>	<i>95% CI</i>		<i>Risk</i>	<i>95% CI</i>		<i>Risk</i>	<i>95% CI</i>	
Average	3.3%	2.2	4.4	1.9%	0.7	3.2	3.6%	2.4	4.8	6.8%	2.6	11.1
No prev. Thrombosis	3.0%	1.3	4.6	1.8%	0.3	3.2	3.3%	1.5	5.0	6.1%	2.0	10.2
Prev. Thrombosis	4.5%	1.1	7.9	2.7%	0.6	4.7	5.0%	1.0	8.9	9.3%	0.0	19.7

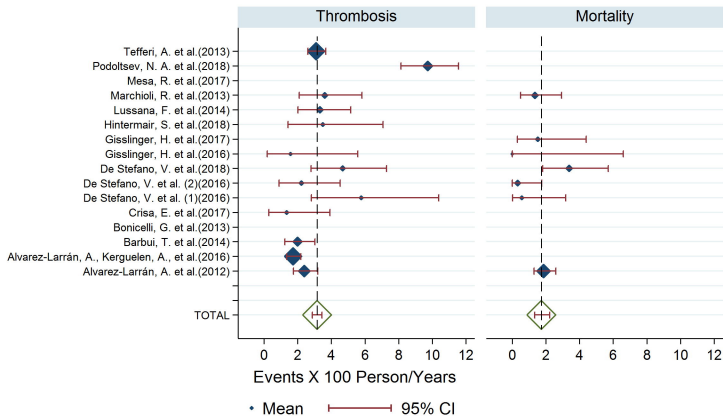
[Captions]

Figure 1: Study flowchart

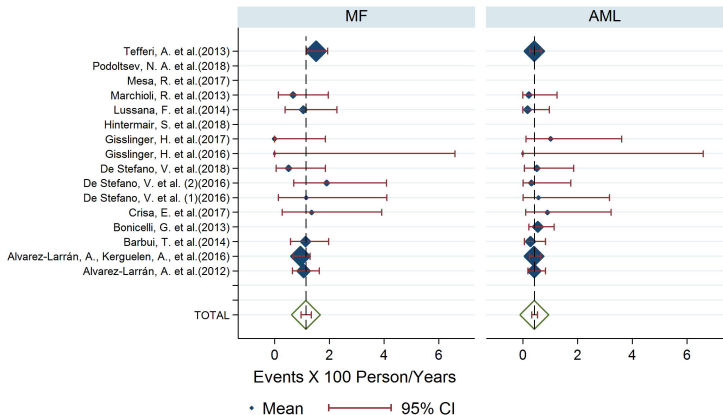
Figure 2: Forest plot of outcomes incidences. The incidence is not graphed for Mesa et al. since its very large CI couldn't fit in the plot, but is accounted for in global estimates. Size of markers annotates study sample size.

Figure 3: outcomes incidence during follow-up according to logistic GLMM (Generalized Linear Mixed Model) and comparison with negative-binomial model. Dashed lines are 95% CIs, observed frequencies are plotted in hollow circles of size proportional to sample size in person/years. ICCs (Intraclass Correlation Coefficients) and p-values of Likelihood Ratio Tests of random slopes are reported



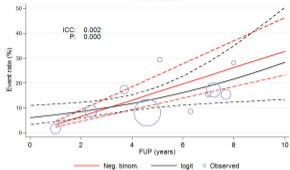


Graphs by outcome_c

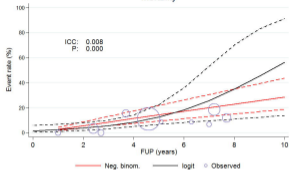


Graphs by outcome_b

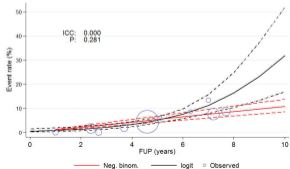
Thrombosis



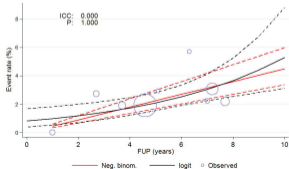
Mortality



MF



AML



Supplementary tables and figures

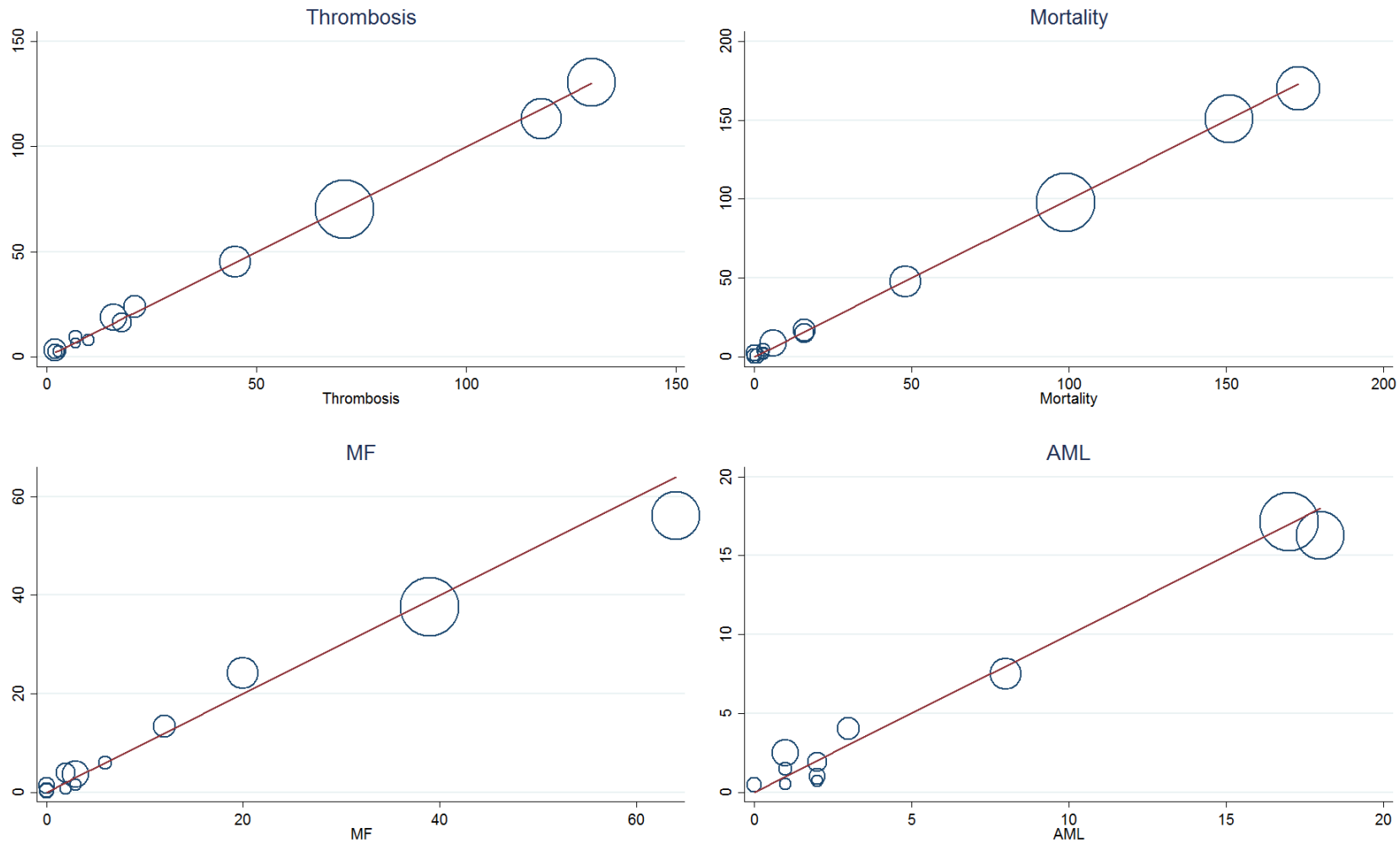
Supplementary Table 1: Logistic models – fixed effects estimates

	OR	P-value	95% CI
Mortality			
Follow-up duration	1.55	0.007**	1.12,2.13
Age	1.21	0.000***	1.09,1.33
Antiplatelet	3.93	0.547	0.05,338.10
Anticoagulant	1.16	0.861	0.22,6.02
CV risk	0.00	0.192	0.00,20.48
Previous thrombosis	1.04	0.968	0.15,7.12
MF			
Follow-up duration	1.55	0.000***	1.31,1.83
Age	1.06	0.021*	1.01,1.11
AML			
Follow-up duration	1.21	0.001***	1.08,1.36
Age	1.02	0.336	0.98,1.07
Thrombosis			
Follow-up duration	1.20	0.016*	1.03,1.39
Age	1.13	0.000***	1.08,1.19
Antiplatelet	5.30	0.156	0.53,53.06
Anticoagulant	1.51	0.323	0.67,3.42
CV risk	0.00	0.001***	0.00,0.04
Previous thrombosis	2.08	0.174	0.72,5.99

Exponentiated coefficients

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Observed vs fitted



Supplementary Figure 1: observed vs fitted plots of logistic GLMM for each outcome. Circle sizes are weighted by study dimension. Predicted values are in good agreement with observed events.