Supplementary Online Content

Biffi A, Anderson CD, Battey TWK, et al. Association between blood pressure control and risk of recurrent intracerebral hemorrhage. *JAMA*. doi:10.1001/jama.2015.10082.

eMethods
eTable 1. Bivariate and Multivariate Analyses of Factors Associated With Recurrent ICH, After Inclusion of Participants With Missing BP Measurements
eTable 2. Bivariate and Multivariate Analyses of Inadequate BP Control Association With Recurrent ICH, Restricted to Subjects with BP Measurements Derived From Medical Records Only
eTable 3. Bivariate and Multivariate Analyses of Factors Associated With Recurrent ICH, After Inclusion of Participants With Discordant EMR vs. Self-Report Follow-up Medication Data
eTable 4. Multivariate Analyses of Factors Associated With Recurrent ICH, After Adjustment for Number and/or Class of Anti-Hypertensive Agents
eFigure. Blood Pressure Capture and Analysis Methods

This supplementary material has been provided by the authors to give readers additional information about their work.

LIST OF ABBREVIATIONS:
ADLs = Activities of Daily Living
BP = Blood Pressure
CT = Computerized Tomography
DBP = Diastolic Blood Pressure
HR = Hazard Ratio
IADLs = Instrumental Activities of Daily Living
ICH = Intra-Cerebral Hemorrhage
IQR = Inter-Quartile Range
JNC7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of
High Blood Pressure
mRS = modified Rankin Scale
NIH = National Institutes of Health
NIHSS = National Institutes of Health Stroke Scale
OMB = Office for Management and Budget
PH = Proportional Hazards
SBP = Sytolic Blood Pressure
TICS = Telephone Interview for Cognitive Status
VIF = Variance Inflation Factor

eMethods

Enrollment Procedures
ICH patients or their guardians / surrogate decision makers were contacted for consideration of enrollment in our longitudinal ICH follow-up cohort within 24 hours of admission with new diagnosis of primary ICH. All participants in the present study were thus enrolled within 24 hours of presentation. Trained study staff obtained written informed consent for participation in this study from all patients or guardians / surrogate decision makers. An enrollment in-person interview and review of medical records were then conducted to capture detailed information on:
- Demographics:
    - Age: self-reported (confirmed by study staff with medical records, identification information)
    - Sex: self-reported
    - Race/Ethnicity: self-reported from categories recommended by the OMB for all NIH-funded clinical research with patients (http://www.whitehouse.gov/omb/fedreg_1997standards).
    - Education: self-reported (in number of years or highest education title achieved)
- Past medical history: self-reported (cross-checked by study staff with admission information and electronic medical records for patients already receiving care within our academic hospital network).
    Specific conditions directly enquired about regardless of self-report included:
    - prior ICH (before current event), including location
    - prior ischemic stroke (imaging confirmed)
    - prior TIA
    - cognitive impairment (any severity)
    - coronary artery disease
    - diabetes mellitus
    - hypertension
    - dyslipidemia (any type of serum lipid fraction abnormality)
    - atrial fibrillation
- Pre-ICH medication exposures: self-reported (cross-checked by study staff with admission information and electronic medical records for patients already receiving care within our academic hospital network).
- Pre-ICH functional status:
    - via structured questionnaire to determine pre-ICH mRS
    - via structured questionnaire to identify dependence for ADLs
    - via structured questionnaire to identify dependence for IADLs
- Acute ICH clinical presentation information:
    - Time from symptoms' onset to ED arrival: obtained from ED medical records
    - Presentation NIHSS: obtained from admitting neurology attending physician notes
    - Information on admission (within 24 hours) CT availability

In order to be considered eligible for further follow-up patient required (at a minimum): complete demographic information (as above), past medical history data (reconciled information from self-report and medical records), pre-ICH medication exposure data, pre-ICH mRS, and admission NIHSS. For all patients with prior ICH before enrollment event, medical records and imaging were obtained to determine location and clinical severity of preceding event. All study participants were then re-evaluated in person at 3 months after ICH, in the setting of a clinical visit including general physical and neurological examination, BP measurements, laboratory studies as deemed necessary by the attending physician and (where applicable) additional neuroimaging.

Follow-up Protocols and Blood Pressure Data Capture
Patients were contacted via phone interview at 3, 9, 12 months after index ICH, and every 6 months thereafter months by certified study staff having undergone dedicated training. During the follow-up phone calls, study staff inquired about recurrent ICH events (if otherwise not identified), incident ischemic stroke, incident dementia, incident dependence for ADLs or IADLs, or death if contacting guardian / legal proxy for deceased patient. In case of death, relevant information (including radiographic reports and/or autopsy reports) was obtained about cause of death from guardian / legal proxy. We also queried the Social Security Death Index (SSDI) national database as an alternative way of identifying deaths among ICH survivors. SSDI querying is performed by trained study staff on all patients currently enrolled every 3-6 months. Identification of a non-recorded death event via SSDI triggered a one-time follow-up phone call (regardless of follow-up schedule) for confirmation of patient death and ascertainment of cause of death. Relevant records were also retrieved, either via EMR review or from former guardians / care-givers of deceased ICH patients contacted by phone.

Study staff also obtained the following information:
- updated medication exposure data (cross-checked by study staff with electronic medical records)
- global cognitive functioning (using the TICS questionnaire)
- dependence for ADLs (via structured questionnaire)
- dependence for IADLs (via structured questionnaire)

Finally, study staff inquired about measured SBP and DBP values.
In order to qualify for recording, recalled BP measurements had to be:
- Obtained by a medical provider (MD, MA, PA, NP or RN)
- Obtained in a medical setting: inpatient hospital facility, rehabilitation facility, emergency department, urgent care clinic, primary care clinic, or outpatient specialist clinic
- Obtained since prior telephone follow-up call
- Consist of precisely recalled SBP AND DBP

If subjects could recall BP measurements being taken, but not their exact value two strategies for data capture were employed:
- For BP measurements reportedly obtained at our institution or affiliated medical facility, EMR was queried to retrieve medical data

- For BP measurements reportedly obtained outside our institution, patients were asked to retrieve relevant medical records and provide them via phone (next follow-up phone call), fax or mail at patients' discretion.

A total of 29,742 SBP/DBP measurements were recorded and available for analysis in the present study. A total of 893 of 1145 study participants (78%) had 100% of BP measurements recorded in the MGH EMR system or other medical records, for a total of 18,737 out of 29.742 BP measurements (63%). Multivariate analyses of BP exposures with recurrent ICH restricted to patients with all BP measurements obtained from medical records are presented in Supplementary Table 2. There were no study participants with 100% BP measurements obtained from telephone-based self-report. The highest percentage of self-reported BP measurements was 3 out of 10 (30%), while the highest self-reported BP measurements count was 7 out of 25 (28%). Among 18,737 BP measurements obtained from medical records, a total of 9,433 (32% of all study BP measurements) had simultaneously obtained values from patient self-report over the phone. Among these BP measurements, we noted good correlation between medical records and patient self-report for both SBP (Spearman's correlation coefficient 0.83, $p < 0.001$) and DBP (Spearman's correlation coefficient 0.75, $p < 0.001$). Median absolute SBP difference in mmHg between medical records and self-report value was 4 mmHg (IQR 0 – 10). Median absolute DBP difference in mmHg between medical records and self-report value was 3 mmHg (IQR 0 – 7).

Absolute Event-Rate Determination
We calculated absolute event-rates in the adequate vs. inadequate BP control groups by first calculating for each individual the amount of time spent in each category (based on SBP / DBP measurements). We generated the total amount of person / years spent in each category by summing all individual contributions across the entire dataset. Individual ICH events were then assigned to the adequate vs. inadequate BP control groups based on the last available SBP/DBP measurements at time of censoring (due to ICH recurrence). Event rates are reported separately for the adequate vs. inadequate BP control groups in no. of events / person-years.

Multivariate Statistical Analyses
We performed bivariate analysis of association between collected baseline and follow-up variables (Table 1, main manuscript) and ICH recurrence. These analyses were carried out using the Log-rank test for bivariate time-to-event analyses. Variables with $p < 0.20$ were retained for inclusion into an initial multivariate model, into which they were entered at the same time. Separate models were created for lobar and non-lobar ICH, and within these two groups four separate models were tested based on different BP exposure variables included (i.e. adequate vs. inadequate BP control, JNC7 hypertension stage, continuous SBP measurements, or continuous DBP measurements).
Multi-collinearity was tested by computing a VIF for each variable in the initial full models. Covariates with VIF > 5 were selected for removal from the model; however no variable in any model fulfilled this criterion. We then applied backward elimination to remove sequentially variable with $p > 0.05$ for association with ICH recurrence risk. Variables were removed one at a time; association statistics were re-calculated at each

step, as were VIFs to check for unmasking of latent multi-collinearity (no variable fulfilled VIF-based criteria for removal). Backward elimination was repeated iteratively until minimal models containing only variables with $p < 0.05$ for association with ICH recurrence were thus generated.

Minimal model generation resulted in the following covariates being retained for analyses (identical covariates regardless of specific BP exposure metrics being tested):

- Lobar ICH: Lobar ICH prior to index event, Antiplatelet Agent Use, Education status
- Non-lobar ICH: Non-lobar ICH prior to index event, Ischemic Heart Disease, African American race (vs. White), Education status

Detailed association testing results for these covariates in the Adequate vs. Inadequate BP control multivariate model are reported in Table 3 (main manuscript).

Next we determined model fit by computing Harrell's C-statistic for all models. We then identified all variables that failed to be retained in the model but showed multivariate $p < 0.10$ for association with ICH recurrence. These were reintroduced in the minimal model, and retained regardless of association p-value if their inclusion resulted in Harrell's C increase > 5% (thus suggesting overall model fit benefit regardless of individual p-values). Antiplatelet exposure in all non-lobar ICH models fulfilled these criteria and was retained in the final models (antiplatelet exposure in lobar ICH was already included in minimal models with all p-values < 0.05). Warfarin exposure fulfilled criteria in all lobar and non-lobar ICH models, and was thus retained for analysis. We pre-specified forced re-inclusion of both antiplatelet and warfarin exposures on the basis of known biological relevance for ICH recurrence, but these variables were already retained in the models due to model fit enhancement as described above. Having fulfilled these steps, final multivariate models were generated.

After generation of final models, the PH assumption was tested by via graphical checks (inspection of Kaplan-Meier curves) and Schoenfeld residuals-based tests (threshold $p < 0.05$ to identify PH assumption violation). All models were found to fulfill the PH assumption using both methods.

ICH Recurrence Risk Estimation

Estimation of ICH Recurrence risk based on average SBP / DBP was performed to provide a summary graphical representation of association testing results, and made use of the *predictSurvProb* function in the *pec* R package (R v. 3.2.0). In order to model ICH recurrence risk, patients were first subdivided in groups based on average observed SBP and SBP. Subjects received two separate category assignment based on SBP and DBP. We then calculated the study-wide risk of lobar ICH and non-lobar ICH using the Nelson-Aalen cumulative hazard estimator function. Estimates were obtained separately for lobar ICH and non-lobar ICH, in light of significantly different recurrence rate (see main manuscript).

Next, we identified variables (other than SBP and DBP) associated with each ICH recurrence outcome (see above for selection criteria, and Tables 3 and 4 in main manuscript for additional details). Each variable was assigned a weight based on Cox-model derived effect size on ICH recurrence, as identified by an HR. For each patient, individual cumulative ICH recurrence risk during follow-up was calculated by modifying

the baseline cumulative Hazard via application of weights representing HR. As a result, each study participants was assigned a percentage risk value for ICH recurrence during follow-up, ranging from 0 to 100%. Predicted risk was then subdivided by length of follow-up (in no. of years) to account for disparity in follow-up duration. This generated an individual-level predicted risk of yearly ICH recurrence, again ranging from 0 to 100%. Actual observed values ranged from 1.7 % to 22.1% / year for lobar ICH, and from 1.0% to 14.5% for non-lobar ICH.

Predicted yearly ICH recurrence risk values were then grouped based on average SBP / DBP category assignments, and their distribution plotted in Microsoft Excel using box-plot with conventions described in the legend for Figure 2 (main manuscript). In each BP-identified group, variations in yearly recurrence risk are dependent on individuals' combinations of other covariate contributing to ICH recurrence risk, with subjects possessing an higher number of associated factors having placing higher in the distribution.

eTable 1. Bivariate and Multivariate Analyses of Factors Associated With Recurrent ICH, After Inclusion of Participants With Missing BP Measurements (n = 49)

Lobar ICH (n = 526) [†]						
Variable	**Bivariate Analysis**			**Multivariate Analysis**		
	HR	**HR 95% CI**	**p value**	**HR**	**HR 95% CI**	**p value**
Inadequate BP Control*	3.21	1.43 – 7.21	**0.005**	3.55	1.65 – 7.66	**0.001**
Non-Lobar ICH (n = 668) [‡]						
Variable	**Bivariate Analysis**			**Multivariate Analysis**		
	HR	**HR 95% CI**	**p value**	**HR**	**HR 95% CI**	**p value**
Inadequate BP Control*	4.02	1.12 – 14.45	**0.034**	4.20	1.07 – 16.50	**0.041**

Bivariate and Multivariate analyses were performed after forced inclusion of 49 patients with no available BP measurements in at least one 6 months follow-up period. BP data missingness was handled by assigning patients the last available measurement prior to missing values (last value carry-over method).

* Defined as a time-varying dichotomous yes/no variable based on whether study participants achieved BP goals recommended by the American Heart Association / American Stroke Association (AHA/ASA) for post-ICH secondary prevention (i.e. SBP < 140 and DBP < 90 if no evidence of diabetes, SBP < 130 and DBP < 80 for diabetic individuals). Please see methods section for additional details.

† All models adjusted for: Lobar ICH prior to Index Event, Antiplatelet Agent Use, Warfarin Use, Education (< 10 years vs. ≥ 10 years)

‡ All models adjusted for: Non-lobar ICH prior to Index Event, Antiplatelet Agent Use, Warfarin Use, Ischemic Heart Disease, African-American Race, Education (< 10 years vs. ≥ 10 years)

95% CI = 95% Confidence Interval for Hazard Ratios, BP = Blood Pressure, ICH = Intra-Cerebral Hemorrhage, HR = Hazard Ratio.

eTable 2. Bivariate and Multivariate Analyses of Inadequate BP Control Association With Recurrent ICH, Restricted to Subjects with BP Measurements Derived From Medical Records Only

Lobar ICH (n = 403) [†]						
Variable	**Bivariate Analysis**			**Multivariate Analysis**		
	HR	**HR 95% CI**	**p value**	**HR**	**HR 95% CI**	**p value**
Inadequate BP Control*	3.69	1.08 – 12.65	**0.039**	3.77	1.18 – 12.08	**0.026**
Non-Lobar ICH (n = 490) [‡]						
Variable	**Bivariate Analysis**			**Multivariate Analysis**		
	HR	**HR 95% CI**	**p value**	**HR**	**HR 95% CI**	**p value**
Inadequate BP Control*	4.10	1.06 – 15.87	**0.042**	4.44	1.04 – 19.01	**0.046**

Bivariate and multivariate analyses of association between Inadequate BP control and recurrent ICH were restricted to 893 of 1145 study participants (78%) who had 100% of BP measurements recorded in the MGH EMR system or other medical records.

* Defined as a time-varying dichotomous yes/no variable based on whether study participants achieved BP goals recommended by the American Heart Association / American Stroke Association (AHA/ASA) for post-ICH secondary prevention (i.e. SBP < 140 and DBP < 90 if no evidence of diabetes, SBP < 130 and DBP < 80 for diabetic individuals). Please see methods section for additional details

† All models adjusted for: Lobar ICH prior to Index Event, Antiplatelet Agent Use, Warfarin Use, Education (< 10 years vs. ≥ 10 years)

‡ All models adjusted for: Non-lobar ICH prior to Index Event, Antiplatelet Agent Use, Warfarin Use, Ischemic Heart Disease, African-American Race, Education (< 10 years vs. ≥ 10 years)

95% CI = 95% Confidence Interval for Hazard Ratios, BP = Blood Pressure, ICH = Intra-Cerebral Hemorrhage, HR = Hazard Ratio.

eTable 3. Bivariate and Multivariate Analyses of Factors Associated With Recurrent ICH, After Inclusion of Participants With Discordant EMR vs. Self-Report Follow-up Medication Data (n = 15)

Lobar ICH (n = 510) [†]						
Variable	Bivariate Analysis			Multivariate Analysis		
	HR	HR 95% CI	p value	HR	HR 95% CI	p value
Inadequate BP Control*	3.20	1.41 – 7.25	**0.006**	3.53	1.65 – 7.63	**0.002**
Non-Lobar ICH (n = 650) [‡]						
Variable	Bivariate Analysis			Multivariate Analysis		
	HR	HR 95% CI	p value	HR	HR 95% CI	p value
Inadequate BP Control*	4.00	1.15 – 13.75	**0.028**	4.23	1.01 – 17.51	**0.047**

Bivariate and multivariate analyses were performed after forced inclusion of 15 patients with at least one discrepant data point about medication exposure during follow-up, when comparing EMR vs. self-report data. Data discordance was handled by assigning patients EMR-derived information.

* Defined as a time-varying dichotomous yes/no variable based on whether study participants achieved BP goals recommended by the American Heart Association / American Stroke Association (AHA/ASA) for post-ICH secondary prevention (i.e. SBP < 140 and DBP < 90 if no evidence of diabetes, SBP < 130 and DBP < 80 for diabetic individuals). Please see methods section for additional details.

† All models adjusted for: Lobar ICH prior to Index Event, Antiplatelet Agent Use, Warfarin Use, Education (< 10 years vs. ≥ 10 years)

‡ All models adjusted for: Non-lobar ICH prior to Index Event, Antiplatelet Agent Use, Warfarin Use, Ischemic Heart Disease, African-American Race, Education (< 10 years vs. ≥ 10 years)

95% CI = 95% Confidence Interval for Hazard Ratios, BP = Blood Pressure, ICH = Intra-Cerebral Hemorrhage, HR = Hazard Ratio.

eTable 4. Multivariate Analyses of Factors Associated With Recurrent ICH, After Adjustment for Number and/or Class of Anti-Hypertensive Agents

Variable: Inadequate BP Control*	Lobar ICH (n = 505) [†]			Non-Lobar ICH (n = 640) [‡]		
	Multivariate Analysis			Multivariate Analysis		
	HR	HR 95% CI	p value	HR	HR 95% CI	p value
- adjusted for No. of anti-HTN agents	3.50	1.60 – 7.68	**0.002**	4.20	1.03 – 17.17	**0.047**
- adjusted for Class of anti-HTN agents	3.46	1.68 – 7.14	**0.001**	4.08	1.04 – 16.08	**0.046**
- adjusted for Class and No. of anti-HTN agents	3.49	1.66 – 7.34	**0.001**	4.16	1.11 – 15.64	**0.036**

Multivariate analyses of association between inadequate BP control and ICH recurrence were performed after adjustment for number, class or number + class of anti-hypertensive agents patients were exposed to during follow-up. Number of agents expressed as categorical variable with levels identifying exposure to 0, 1, 2, or $\geq$ 3 agents (0 group used as reference). Class of agents expressed as separate dichotomous variables for beta-blockers, ACE Inhibitors, Calcium-Channel Blockers, Diuretics or Other (no exposure group used as reference). Joint adjustment for number and class of anti-hypertensive agents employed both methods in the same multivariate model.

* Defined as a time-varying dichotomous yes/no variable based on whether study participants achieved BP goals recommended by the American Heart Association / American Stroke Association (AHA/ASA) for post-ICH secondary prevention (i.e. SBP < 140 and DBP < 90 if no evidence of diabetes, SBP < 130 and DBP < 80 for diabetic individuals). Please see methods section for additional details.

† All models also adjusted for: Lobar ICH prior to Index Event, Antiplatelet Agent Use, Warfarin Use, Education (< 10 years vs. $\geq$ 10 years)

‡ All models also adjusted for: Non-lobar ICH prior to Index Event, Antiplatelet Agent Use, Warfarin Use, Ischemic Heart Disease, African-American Race, Education (< 10 years vs. $\geq$ 10 years)

95% CI = 95% Confidence Interval for Hazard Ratios, anti-HTN = anti-hypertensive, BP = Blood Pressure, ICH = Intra-Cerebral Hemorrhage, HR = Hazard Ratio, No. = number.

eFigure. Blood Pressure Capture and Analysis Methods
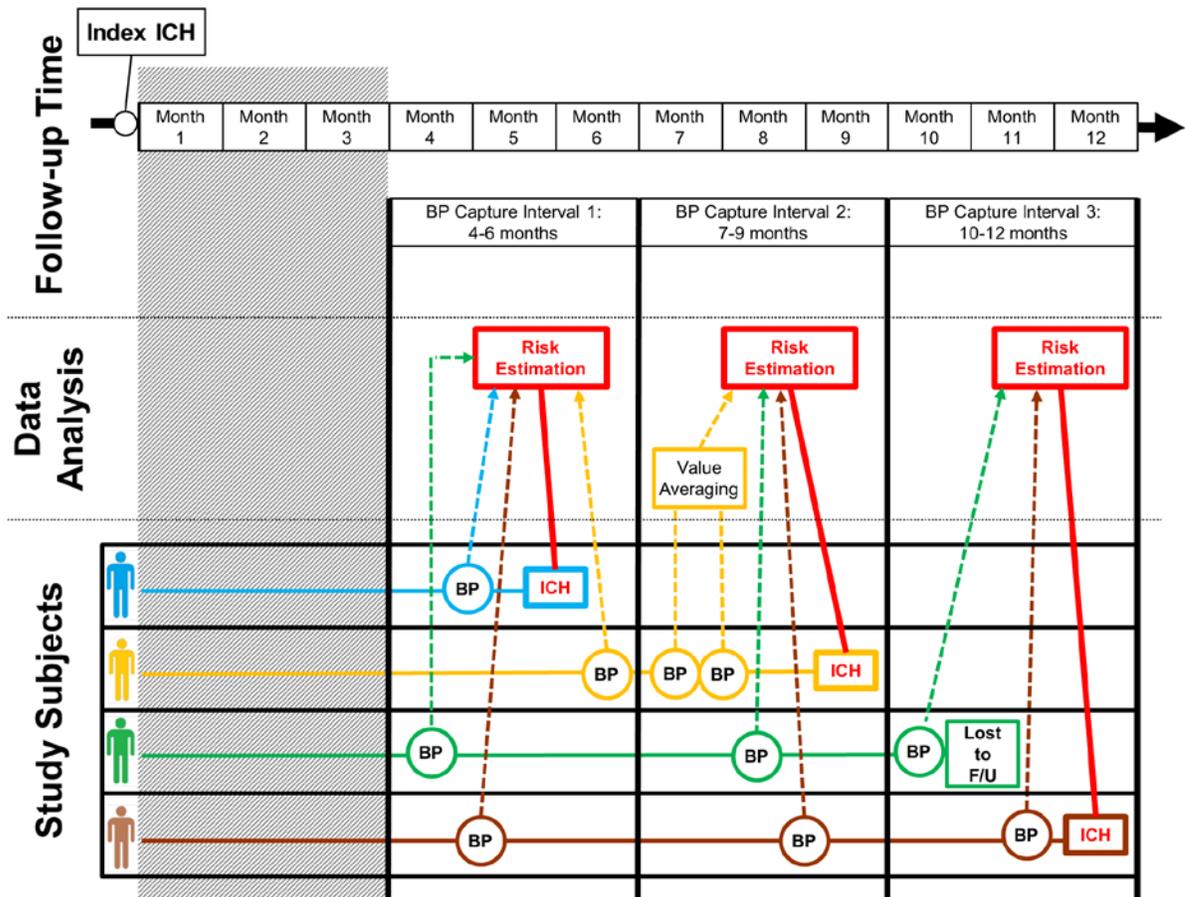
The top-most panel depicts the first 12 months of follow-up time; the shaded area represents the left-censoring of data in the first 90 days (to avoid analyzing early re-bleeding events). Follow-up time is subdivided in 3-months interval as shown (BP capture interval 1: 4-6 months, interval 2: 7-9 months, interval 3: 10-12 months). Four study individuals are schematically presented and identified by different colors in the bottom panel. For each individual, BP measurements are represented by non-filled colored circles labeled "BP". Recurrent ICH (non-filled colored boxes labeled "ICH) represents a failure event in the Cox model multivariate analysis, and thus triggers re-estimation of recurrent ICH risk among all patients still in the study (analysis presented in red boxes in the middle panel). All BP measurements in the same BP data capture interval contribute to analysis (see recurrent ICH for blue patient in interval 1). When multiple BP values are available in a single interval, the average value is used for analysis purposes (value averaging for yellow patient BP measurements interval 2). Study participants lost to follow-up (green patient in interval 3) can contribute all BP measurements pre-dating loss to follow-up to the analysis (as in the analysis triggered by recurrent ICH for dark brown patient in interval 3). A similar scheme is applied after the first 12 months of follow-up, except BP capture interval are dilated to encompass 6 months each (i.e. 13-18 months, 19-24 months, etc.).