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**Running head:** LONG-TERM WEGENT TRIAL OUTCOMES FOR AAV  
MAINTENANCE THERAPY

**Long-Term Outcomes of the WEGENT Trial on Remission-Maintenance  
for Granulomatosis with Polyangiitis or Microscopic Polyangiitis**

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## ABSTRACT

**Objective.** The WEGENT trial and other short-term studies suggested that azathioprine or methotrexate could effectively maintain granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) remission. Whether differences in relapse or adverse event rates would appear after discontinuation of those 2 maintenance regimens and longer follow-up remains unknown.

**Methods.** Long-term outcomes for the patients enrolled in the WEGENT trial were analyzed according to their randomization group. Parameters at trial entry were evaluated as potential prognostic factors for death, relapse or damage in multivariate models.

**Results.** Data were returned for 88.8% of the 126 original participants. Median [95% confidence interval] followup was 11.9 [11.3–12.5] years. For the azathioprine and methotrexate arms, respectively, the 10-year overall survival rates were 75.1% [64.8–86.9] and 79.9% [70.3–90.8] ( $P = 0.56$ ), and relapse-free survival rates 26.3% [17.3–40.1] and 33.5% [23.5–47.7] ( $P = 0.29$ ). No between-arm differences were observed for relapse, adverse events, damage, survival rates without severe side effects and survival rates without relapse and severe side effects. Considering only the 97 GPA patients, no between-arm survival differences were observed. Relapse-free survival was shorter for GPA than MPA patients but the multivariate analysis retained anti-PR3–ANCA-positivity, and not GPA, as being independently associated with relapse.

**Conclusion.** This long-term analysis confirms that azathioprine and methotrexate are comparable options for maintaining GPA or MPA remission. Despite good overall survival, relapses, adverse events and damage remain matters of concern and further studies are needed to reduce them.

The introduction of cyclophosphamide (CYC) and glucocorticoids in the 1950s dramatically improved prognoses of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAVs) (1). For granulomatosis with polyangiitis (Wegener's) (GPA), 74–80% of patients now survive 5 years (2–4), compared with ~70% 1-year mortality for untreated patients (5). Similarly, for microscopic polyangiitis (MPA), the 5-year survival rate reaches 65–95%, depending on the prognostic factors considered (6–8). However, those advances were achieved at the cost of treatment-related toxicity (9).

The development of a 2-staged approach, using CYC (10), and later rituximab (11,12), for induction, and a less toxic remission-maintenance regimen to limit cumulative CYC exposure, was a major step forward in GPA and MPA treatment. Maintenance usually combines low-dose glucocorticoids and azathioprine (AZA) or methotrexate (MTX) (10–18). The prospective, multicenter, randomized, open-label, WEGENT trial, conducted by the French Vasculitis Study Group, evaluated the safety and efficacy of AZA versus MTX, combined with prednisone, as maintenance therapy for severe GPA or MPA, after complete remission had been achieved with glucocorticoids and pulse intravenous CYC (18). Trial results demonstrated that MTX was as safe and effective as AZA at maintaining GPA or MPA remission during 29 months of followup. Thus, either agent has emerged as standard care for AAV-remission maintenance (19).

However, it remains unknown whether differences in relapse or adverse event rates would appear after discontinuation of those 2 maintenance regimens and longer followup. The aim of this followup study was to evaluate the long-term outcomes of WEGENT trial participants to determine whether initial AZA or MTX maintenance might be associated with fewer relapses, less toxicity and better long-term survival. Clinical and laboratory parameters at trial entry were also tested as potential prognostic factors in multivariate models for survival, relapse-free survival, relapse or damage.

## **PATIENTS AND METHODS**

**Study eligibility criteria.** The WEGENT trial was conducted from November 1998 through February 2005 in France and Belgium (18). Briefly, it included patients with newly diagnosed GPA or MPA according to the Chapel Hill nomenclature (20,21). In addition, patients had to have severe GPA, defined as renal disease, involvement of  $\geq 2$  organs or systems, or involvement of 1 organ or system and constitutional symptoms; or severe MPA with  $\geq 1$  poor-prognosis items of the Five-Factor Score (FFS) (serum creatinine  $>140 \mu\text{mol/liter}$ , proteinuria  $>1 \text{ g/day}$ , specific cardiomyopathy, gastrointestinal tract and/or central nervous system involvement) (22).

**Treatment protocol.** All patients received daily intravenous (IV) methylprednisolone for 3 days, followed by oral prednisone (1 mg/kg/day) for 3 weeks, then progressively tapered according to a predefined schedule to obtain complete cessation after 27 months. CYC pulses were administered until remission, followed by 3 additional consolidation pulses. Patients who entered remission were randomized after the 3<sup>rd</sup> consolidation to receive oral maintenance with 12 months of AZA (2 mg/kg/day) or MTX (progressively increased to 25 mg/week). The study primary analysis was conducted when the last enrolled patient completed maintenance therapy, yielding a median followup of 29 months for the entire population. After the end of the study, treatment, including for potential relapses, was left to the treating physician's discretion.

**Evaluations.** The original protocol scheduled long-term analysis at 10 years of followup. Long-term outcomes were ascertained for the 126 enrolled patients. A questionnaire, sent to participating physicians, requested information on survival, relapse, cancer, infection, cardiovascular morbidity, damage, immunosuppressant use and death. Patients' medical charts were also examined to complete discordant or incomplete information. Replies were collected from October 2013 until September 2014. Demographic, clinical and laboratory parameters at inclusion were analyzed in multivariate models as potential prognostic factors for survival, relapse or damage.

This followup study was performed in accordance with the 1964 Declaration of Helsinki

and subsequent amendments. The Île-de-France III Ethics Committee approved the study in accordance with national legislation.

**Study endpoints.** The primary endpoint was defined as the 10-year overall survival. Other judgment criteria were: relapse, major relapse, any adverse event, severe adverse event, infection, damage assessed with the Vasculitis Damage Index (VDI) (23), relapse-free survival and event-free survival, i.e., the probability of surviving without suffering a relapse or severe adverse event.

Vasculitis activity was assessed with the Birmingham Vasculitis Activity Score (BVAS) version 3 (24). The following definitions were applied: remission: the absence of signs of “new/worsening” disease activity, with BVAS = 0 (25); relapse: the reoccurrence or new appearance of disease activity attributable to active vasculitis (26); a major relapse: the reoccurrence or new onset of potentially organ- or life-threatening disease activity that cannot be treated with increased glucocorticoids alone and requires further therapeutic escalation (26). Adverse events were graded 1–4, according to World Health Organization toxicity criteria, with grades 3 and 4 considered severe (27). A serious infection was defined as life-threatening, requiring IV antibiotics or hospitalization.

**Statistical analyses.** All trial participants’ data were analyzed according to the assigned randomization group. Followup began at WEGENT trial inclusion and continued until the last medical update, death or 10 years post-inclusion, whichever occurred first. Events were defined as death, relapses (major or not) and serious adverse events. Frequencies of adverse events, serious adverse events, infections, cancers, relapses and major relapses were compared with robust Poisson regression analyses. Numbers of relapses, major relapses and damaged organs were compared using negative binomial regressions. Those analyses were adjusted to followup time, added as an offset term in the respective models. Overall survival, relapse-free survival and event-free survival were analyzed with the Kaplan–Meier method and compared using log-rank tests.

Demographic, clinical and laboratory parameters at inclusion were analyzed in multivariate



models as potential prognostic factors for survival, relapse-free survival, relapse or damage. Multivariate analyses used Cox models to estimate hazard ratios (HRs) and their confidence intervals (CIs). A multistate model was used to account for multiple relapses per patient and distinguish between the 2 competing events: death and relapse (28). A competing-risk model was used because a disease-severity variable associated with death can also be associated with relapse, meaning that patients with a risk factor for relapse might be censored early due to death in traditional time-to-event analyses, thereby obscuring the association of those risk factors with relapses. Forty-five imputations run for risk-factor evaluation were analyzed in 2 steps: variables with  $P < 0.20$  in a univariate analysis were selected for possible inclusion in the multivariate model, and stepwise selection based on Akaike's information criterion considered all the selected factors in the stacked dataset (29). All analyses were truncated at 10 years of followup and computed with R statistical software v3.0.1 (30).

## RESULTS

Among the 126 patients (median age 61 years) randomized in the original study (Figure 1), 97 (77%) patients had GPA and 29 (23%) MPA. Anti-proteinase-3 (PR3) ANCA were found in 76 (60%) patients, while anti-myeloperoxidase (MPO) ANCA were detected in 39 (31%). Ten-year data were available for 112/126 (88.8%) patients and were missing for 14 after a median followup of 7.0 (interquartile range (IQR) 5.1–9.1) years. Median followup was 11.9 [95% CI 11.4–12.4] years. Clinical outcomes according to treatment group are summarized in Table 1.

**Overall survival.** Fifteen AZA-group and 12 MTX-arm patients died during followup, with, respectively, 1 and 2 deaths during the original trial's followup. The primary endpoint, defined as the 10-year overall survival rate, did not differ significantly for the AZA (75.1%) and MTX arms (79.9%) (Figure 2A and B). Causes of AZA-group deaths, censored at 10 years, included 6 cancers, 3 cardiac causes, 1 alveolar hemorrhage, 1 end-stage renal disease (ESRD), 1

pulmonary embolism, 1 trauma and 2 unknown causes. MTX-arm deaths were attributed to 1 cancer, 4 cardiac causes, 4 infections, 1 ESRD, 1 pulmonary embolism and 1 Alzheimer's disease.

Multivariate analysis retained advancing age as the only factor significantly associated with increased risk of death (HR 1.09 [95% CI 1.05–1.14];  $P < 0.001$ ), with each additional year increasing the probability of death by 9% (Figure 2C). Lung involvement (affecting 75% of our patients at baseline), neurologic, cardiovascular or digestive involvement, impaired kidney function, AAV (GPA versus MPA) (Figure 2D), ANCA status (PR3 versus MPO or no ANCA) and BVAS-assessed disease activity at inclusion had no statistically significant impact on survival.

**Relapses.** During followup,  $\geq 1$  relapses occurred in ~60% of AZA-group and 54% of MTX-arm patients before the 10-year censoring date, with respective first relapses in 31/38 (81.6%) and 30/34 (88.2%) only after terminating maintenance. No between-arm differences were found for the total numbers of relapses and major relapses per patient, and the relapse or major relapse rates. The risk of relapse adjusted to followup duration until the first event was comparable for both arms. Ten-year relapse-free survival rates for the AZA and MTX arms did not differ significantly (Figure 3A).

ANCA status (anti-PR3 versus anti-MPO or no ANCA) was a more powerful predictor of relapse-free survival and relapse than disease subtype (GPA versus MPA) (Figure 3B). Moreover, AAV was not significantly associated with either relapse parameter in multivariate analyses. Neither CYC duration nor cumulative dose was associated with relapse-free survival. In the multistate model accounting for all relapses, baseline anti-PR3–ANCA-positivity was the strongest factor significantly associated with relapses (Table 2). High initial serum creatinine decreased the probability of relapse, with each additional 10  $\mu\text{mol}$  of creatinine/liter lowering the relapse risk by 1%. The glucocorticoid dose at the end of maintenance therapy or thereafter increased that risk. In this multivariate model, AAV, its BVAS-assessed activity at baseline and

the CYC pulse number or cumulative dose (g) for remission-induction before randomization did not affect the relapse rate.

**Adverse events.** During the 10-year censored followup, no long-term between-arm differences were observed for severe adverse events, serious infections or cancer.

Thirty-three (26%) patients developed serious infections requiring hospitalization, with the infection leading to the deaths of 4 (3%) of them. The 10-year AZA-group and MTX-arm severe side-effect-free and event-free survival rates were comparable.

During long-term followup, the following cancers were observed: in the AZA arm: 6 adenocarcinomas, including 3 colorectal, 1 stomach, 1 breast and 1 ovarian cancer; 1 bladder cancer (after a cumulative total CYC dose of 8 g); 1 squamous cell carcinoma of the lung; 1 cerebral glioblastoma; 1 cutaneous melanoma and 1 cutaneous basal cell cancer; in the MTX arm: 5 adenocarcinomas, including 2 colorectal, 2 ovarian and 1 uterine cancer; 1 small-cell lung carcinoma; 1 hepatocellular carcinoma without viral hepatitis infection; 1 cutaneous squamous cell carcinoma and 1 cutaneous basal cell carcinoma.

**Duration of immunosuppression.** All patients received their assigned AZA or MTX maintenance according to the trial protocol for comparable times and glucocorticoid durations of intake were also similar for the 2 arms. Table 3 summarizes the post-trial treatments patients received during long-term followup. Neither the numbers of treated patients nor the estimated mean cumulative cyclophosphamide or rituximab doses for AAV relapse differed significantly between arms.

At the last update for AZA and MTX arms, respectively, data on glucocorticoids and other immunosuppressants were missing for 8 and 6 patients; 29 patients in each group were still taking prednisone (median respective doses: 7.0 and 5.0 mg/day); 20 and 18 patients were still taking other immunosuppressants, mainly MTX (12 patients), rituximab (11 patients) and AZA (8 patients); and, finally, 28 and 27 patients were no longer taking any immunosuppressant.

**Renal function.** No significant between-arm difference was observed for renal function or

ESRD, with 7 (11.1%) AZA-group and 8 (12.7%) MTX-arm patients developing ESRD. Although all these 15 patients had initial renal involvement, 3 of them had creatinine <100  $\mu\text{mol/liter}$  at inclusion. Those 15 patients had 24 relapses, 16 of which included renal involvement. In addition, 4 patients required transient dialysis at AAV onset or at relapse; with median follow-up of 11 years, their mean  $\pm$  SD creatinine value and glomerular filtration rate (GFR) at last follow-up was  $159 \pm 27 \mu\text{mol/liter}$  and  $34 \pm 6 \text{ ml/min}$ , respectively.

Among the 93 (47 AZA and 46 MTX, respectively) patients without ESRD and whose renal parameters were available at last update, mean serum creatinine levels ( $111.4$  [range 55–273] and  $105.9$  [range 49–276]  $\mu\text{mol/liter}$ ) and mean GFR ( $59.5$  and  $61.3 \text{ ml/min}$ ) did not differ significantly.

**Damage.** At the last update, accrued damage was severe in both arms but mean VDI scores were similar for the 2 study arms. Multivariate analysis adjusted to followup duration retained age, baseline anti-PR3–ANCA-positivity versus anti-MPO–ANCA or none, initial creatinine level and glucocorticoid dose at the end of the maintenance as being significantly associated with VDI-assessed damage (Table 2).

**Survival analysis of GPA patients alone and versus MPA patients.** Considering only the 97 GPA patients, the AZA and MTX arms did not differ significantly for overall survival, relapse-free survival, survival without major relapse, survival without severe side effects or event-free survival.

For GPA versus MPA, respectively, the 10-year overall survival rates ( $75.1\%$  [95% CI 66.8–84.5] and  $85.2\%$  [95% CI 72.8–99.8]) did not differ significantly (HR 1.84 [95% CI 0.64–5.33]) (Figure 2D). Ten-year relapse-free survival was shorter for GPA than MPA patients ( $23.3\%$  [95% CI 16.2–33.7] versus  $51.7\%$  [95% CI 36.4–73.5], respectively; HR 2.20 [95% CI 1.24–3.91];  $P = 0.007$ ) but multivariate analysis did not retain GPA as being independently associated with relapse.

## DISCUSSION

The WEGENT trial was undertaken to compare the safety and efficacy of MTX versus AZA as GPA or MPA remission-maintenance therapy. Both drugs appeared to be equivalent alternatives to maintain remission at 29 months and our long-term analysis results further confirm our original findings (18). Whereas overall survival was good, relapses, adverse events and damage were common.

Survival of our severe GPA patients is consistent with previous studies, but 10-year survival data for MPA patients were lacking. The prolonged followup of WEGENT-trial patients yielded 10-year overall survival rates of 75.1% for GPA and 85.2% for MPA patients, comparable to the 80% reported for the 158 GPA patients enrolled in the NIH cohort study but after mean followup of only 8 years (9); 75% for the 56 GPA patients included in another study (2); and 88% for a cohort of 155 consecutive GPA patients (followup 6.6 years), 24 with localized disease (31), and 86% of 148 GPA patients (followup 4 years), 18 with localized disease, participating in a single-center cohort study (32). Reported 5-year survival of MPA patients ranged between 45% and 76% in 5 studies that included 217 MPA patients (33). The higher MPA survival rate observed herein, despite the inclusion of only patients with severe disease (FFS  $\geq 1$ ), fully supports the usefulness of therapy adapted to the prognostic FFS and further validates it for severe MPA.

In our long-term study, overall survival was comparable for GPA and MPA patients, in accordance with another large, long-term study (34). Differences noted in earlier investigations (35,36) may have reflected either the reporting of crude mortality, without adjusting for MPA patients' older age, underpowered multivariate analyses and/or inadequate case-mix (34).

According to our multivariate analysis, advancing age was the sole factor significantly associated with death, as identified in previous GPA studies (2,3,31). The only other study that identified prognostic baseline factors for survival in a cohort of GPA patients receiving homogeneous care found age, kidney and lung involvement to be associated with poorer survival

(31). For MPA, age, renal and severe gastrointestinal involvement were reported to be the main significant indicators of diminished survival (6,37). All those are items included in the revised FFS, which is also applicable to GPA and MPA (38).

Although the induction-maintenance approach to treat GPA and MPA undoubtedly represents an important therapeutic advance, the frequent relapses (half to two-thirds of our participants at 10 years) still pose a challenge for their long-term management. Indeed, 10-year relapse-free survival was only 26.3% and 33.5% for the AZA and MTX recipients, respectively. These low rates are consistent with other long-term studies on GPA (24% at 5 years) (39) and MPA (45.4% and 43.4% at 7 years) (7,8). Anti-PR3-ANCA-positivity has repeatedly been shown to be associated with a higher relapse risk for AAV cohorts (40–43) or other randomized-controlled trials (44–46), in agreement with our findings. Although GPA patients reportedly relapsed more frequently than those with MPA (10), it must be emphasized that our multivariate analysis retained baseline anti-PR3-ANCA-positivity, but not GPA, as being independently and significantly prognostic of recurrent relapses and, thus, negatively affected relapse-free survival. Thus, the more frequent cumulative GPA relapses might be linked to the more frequent presence of those antibodies in these patients. This notion supports those found in a study including patients with renal disease (42). Our results also retained high serum creatinine levels as being independently associated with significantly fewer relapses. That finding corroborates observations based on 2 large AAV cohorts: relapses of 535 European and 439 Chinese patients were inversely associated with the serum creatinine concentration (43,47). Patients with impaired renal function, who are less prone to relapse but have an increased risk of death due to treatment side effects (48), might be better treated with milder immunosuppression. This hypothesis should be investigated prospectively.

The WEGENT protocol required stopping glucocorticoids after a 2-year total duration. That glucocorticoid dose and duration were associated with heightened risk of relapse in our study might be explained by physicians being more likely to continue glucocorticoids or delay their

dose-tapering, when vasculitis remains in remission but atypical signs or symptoms appear or acute-phase reactants increase, possibly due to an intercurrent affection, or perhaps immediately preceding relapse. Meta-analysis results showed that trials in which glucocorticoids were not scheduled for withdrawal (usually continuing prednisone at 5–7.5 mg/day) or were routinely prescribed for >18 months (mostly European studies) had markedly lower relapse rates than those in which they were discontinued earlier by month 6–12 (including most U.S. studies) (49). On the other hand, our findings demonstrated that glucocorticoid dose at the end of the maintenance was associated with higher accrued damage, consistent with previous observations (2). Thus, optimal glucocorticoid duration needs to be examined in randomized–controlled trials analyzing both relapse rate and accrued damage.

In the WEGENT trial, the study drug had to be discontinued after 12 months of maintenance therapy and >80% of our patients' first relapses in each arm occurred only after treatment withdrawal, as previously reported (9,50). Patients initially anti-PR3–ANCA-positive are at higher risk of relapse and may require longer maintenance therapy to limit this risk. Results of a retrospective study showed, among newly diagnosed GPA patients, that longer maintenance therapy was associated with fewer relapses, even after adjusting for prednisone use (50). Because of limited power, a prospective controlled trial was unable to confirm significantly different relapse-free survival among patients persistently positive for cytoplasm-labeling ANCA at remission randomized to receive either standard or extended maintenance therapy (51). The results of the randomized REMAIN trial, comparing 18–24 months versus 4 years of treatment, should help better define optimal maintenance-therapy duration for different AAVs (52).

Further investigation is needed to optimize maintenance regimens. In our group's recently published randomized–controlled MAINRITSAN trial, the reinfusion of fixed-interval low-dose rituximab (0.5 g every 6 months until month 18) better prevented GPA or MPA relapses than 22 months of azathioprine and represents a significant advance, particularly for anti-PR3–ANCA-positive patients who are more prone to relapse (53).

Severe adverse events remain frequent during the long-term followup of these patients, with a quarter of them developing serious infections. The same percentage was observed in the German cohort (31), as opposed to 46% of the NIH cohort (9). Infection led to the deaths of 3% of our patients, again similar to those reported for the German (31) and NIH cohorts (9).

Our study has several notable strengths. To our knowledge, it has the longest followup among studies investigating survival of patients with MPA or GPA, followed for a median of >11 years post-inclusion in a randomized–controlled trial for newly diagnosed AAV. In addition, data was available for ~90% of the original trial participants. We used competing-risk analysis that may more easily identify some factors associated with relapse and death. Moreover, multiple imputations improved the resulting estimates and decreased bias due to missing data. Furthermore, these patients were recruited from 70 French Vasculitis Network centers and are therefore likely to be representative of the entire vasculitis-patient spectrum. Hence, our findings should be generalizable.

Some limitations also need to be acknowledged. This original trial was not designed to assess the impact of the 2 regimens on long-term relapse or survival. After the year-long maintenance therapy, immunosuppressant use was left to the treating physician. One cannot exclude that a difference between the 2 drugs, in terms of efficacy and/or safety, could be observed at a later date if they were taken for a longer duration. Our study may have been underpowered to detect a higher risk of death associated with initial cardiovascular involvement or severe renal impairment because too few affected patients were included. This long-term followup study was retrospective, with all the inherent potential biases associated with retrospective data collection. However, questionnaire-response rates were high and patients' medical charts were also reviewed to complete discordant or incomplete information, leading to the availability of long-term data for ~90% of the participants. So, despite being retrospective, we think that significant ascertainment bias is unlikely.

In conclusion, this long-term analysis confirms that MTX and AZA are comparable



options for maintaining GPA or MPA remission. Despite good overall survival, relapses, adverse events and damage continue to be persistent concerns in AAV patients. Longer maintenance treatment, at least for anti-PR3–ANCA-positive patients should be evaluated prospectively, as well as newer strategies to decrease relapse and damage rates.

### **AUTHOR CONTRIBUTIONS**

All authors were involved in drafting the article or revising it critically for important intellectual content and all authors approved the final version to be published. Dr. Puéchal had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Puéchal, Pagnoux, Ravaud, Guillevin.

**Acquisition of data.** Puéchal, Pagnoux, Perrodeau, Hamidou, Boffa, Kyndt, Liferman, Papo, Merrien, Smail, Delaval, Hanrotel-Saliou, Imbert, Khouatra, Lambert, Leské, Ly, Pertuiset, Roblot, Ruivard, Subra, Viallard, Terrier, Cohen, Mouthon, Le Jeune, Ravaud, Guillevin.

**Analysis and interpretation of data.** Puéchal, Pagnoux, Perrodeau, Ravaud, Guillevin.

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## APPENDIX

In addition to the authors, the following FVSG investigators and members (listed alphabetically by city) participated in the study (all in France unless specified otherwise): Centre Hospitalier (CH), Agen: P Rispal; CH, Alençon: N Baidi, O Chrétien; CH Universitaire (CHU), Hôpital Nord, Amiens: R Cevallos, J-P Ducroix; Amou: J-G Darmaillacq; CHU, Angers: F Dubas†, M-N Maghakian, C Moreau; CH, Argentan: C Dubos-Arvis; Cliniques du Sud Luxembourg, Arlon, Belgium: R Frogner; CH, Avignon: P Gobert, J Pollini; Beaune: D Pingat; CH, Beaune: L Janin-Manificat; CH, Blois: B Lafon; Hôpital Jean-Verdier, Bondy: A Kettaneh; CHU Pellegrin, Bordeaux: M Moiton, JM Ragnaud; CH, Bourg-en-Bresse: C Boudray, B Raphanel, J-P Renand; CH Pierre-Oudot, Bourgoin-Jallieu: M Roux; Bouzy: G Bonnaire; Branne: A Guiso; CHU, Brest: JM André, R Perrichot; Broglie: J Louvet; CHU Clémenceau, Caen: N Artigues, B Bienvenu, B Hurault de Ligny, C Le Hello, P Letellier, T Lobbedez, Y Ollivier, M Pujo, J-P Ryckelynck; CH René-Dubos, Cergy-Pontoise: J-J Montseny; Champs-sur-Marne: P Collet; CH, Charleville Mézières: B Ayach, J-J Dion, H Mouawad; CH, Chartres: R Damade, L Dupouët; Château Thébaud: K Asgaraly; Chaumont: B Depernet; Hôpital Louis-Pasteur, Cherbourg: T Colin; Hôpital Antoine-Béclère, Clamart: V Ioos; CHU Hôtel-Dieu, Clermont-Ferrand: V Rieu; Hôpital Beaujon, Clichy: N Belmatoug, L Foulon, G Jebrak; CH, Compiègne: L du Coedic; CH Laennec, Creil: C Bachmeyer; CHU Henri-Mondor, Créteil: A Dumoulin, B Godeau, M Khellaf, M Michel, M Pastural, A Schaeffer; Dammartin-en-Goële: M Geffroy; CHU, Dijon: P Bielefeld; CH, Dreux: D Fichet; CH, Eaubonne: J-L Saraux; Groupe Hospitalier Mutualiste, Grenoble: S Vinzio; Jard-sur-Mer: P Ehrlacher; CHU, Kremlin-Bicêtre: A Azria, X Mariette; CH, La Roche-sur-Yon: M Tiab; CH, Laval: D Delansorne; CH, Le Mans: N Boullanger, F Closs-Prophette, A Goldstein; Le Mans: L Bouscaud; CH Robert-Boulin, Libourne: V Meunier; CHU Claude-Huriez, Lille: E Hachulla, P-Y Hatron, D Launay; CHU Dupuytren, Limoges: C Hottelart, E Liozon, O Longuet, V Loustaud-Ratti, P Soria, E Vidal; CH Robert Bisson, Lisieux: L Geffray, P Henri, I Landru; CH Bretagne-Sud, Lorient: J-M Guillemot, J Le Noach; Hôpital Louis-Pradel,

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## REFERENCES

1. Fauci AS, Katz P, Haynes BF, Wolff SM. Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *N Engl J Med* 1979;301:235–8.
2. Koldingsnes W, Nossent H. Predictors of survival and organ damage in Wegener's granulomatosis. *Rheumatology (Oxford)* 2002;41:572–81.
3. Bligny D, Mahr A, Le Toumelin P, Mouthon L, Guillevin L. Predicting mortality in systemic Wegener's granulomatosis: a survival analysis based on 93 patients. *Arthritis Rheum* 2004;51:83–91.
4. Lane SE, Watts RA, Shepstone L, Scott DG. Primary systemic vasculitis: clinical features and mortality. *QJM* 2005;98:97–111.
5. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J* 1958;2:265–70.
6. Guillevin L, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum* 1999;42:421–30.
7. Samson M, Puéchal X, Devilliers H, Ribi C, Cohen P, Bienvenu B, et al. Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without poor-prognosis factors. *Autoimmun Rev* 2014;13:197–205.
8. Samson M, Puéchal X, Devilliers H, Cohen P, Bienvenu B, Ly KH, et al. Long-term follow-up of polyarteritis nodosa and microscopic polyangiitis with poor-prognosis factors (abstract). *Arthritis Rheum* 2014;66,11 Suppl:S782.
9. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488–98.
10. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniené J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil

- cytoplasmic autoantibodies. *N Engl J Med* 2003;349:36–44.
11. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010;363:211–20.
  12. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010;363:221–32.
  13. de Groot K, Reinhold-Keller E, Tatsis E, Paulsen J, Heller M, Nölle B, et al. Therapy for the maintenance of remission in sixty-five patients with generalized Wegener’s granulomatosis. Methotrexate versus trimethoprim/sulfamethoxazole. *Arthritis Rheum* 1996;39:2052–61.
  14. Langford CA, Talar-Williams C, Barron KS, Sneller MC. A staged approach to the treatment of Wegener’s granulomatosis: induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. *Arthritis Rheum* 1999;42:2666–73.
  15. Reinhold-Keller E, Fink CO, Herlyn K, Gross WL, de Groot K. High rate of renal relapse in 71 patients with Wegener’s granulomatosis under maintenance of remission with low-dose methotrexate. *Arthritis Rheum* 2002;47:326–32.
  16. Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener’s granulomatosis: extended follow-up and rate of relapse. *Am J Med* 2003;114:463–9.
  17. Wegener’s Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener’s granulomatosis. *N Engl J Med* 2005;352:351–61.
  18. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 2008; 359:2790–2803.
  19. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann*

- Rheum Dis 2009;68:310–7.
20. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides: the proposal of an international consensus conference. *Arthritis Rheum* 1994;37:187–92.
  21. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013;65:1–11.
  22. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al. Prognostic factors in polyarteritis nodosa and Churg–Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)* 1996;75:17–28.
  23. Exley AR, Bacon PA, Luqmani RA, Kitis GD, Gordon C, Savage CO, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum* 1997;40:371–80.
  24. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009;68:1827–32.
  25. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *QJM* 1994;87:671–8.
  26. Hellmich B, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillevin L, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. *Ann Rheum Dis* 2007;66:605–17.
  27. World Health Organization. WHO Toxicity Criteria by Grade. (accessed at <http://www.fda.gov/cder/cancer/toxicityframe.htm>).
  28. Andersen PK, Keiding N. Multi-state models for event history analysis. *Stat Methods Med Res* 2002;11:91–115.

29. Wood AM, White IR, Royston P. How should variable selection be performed with multiply imputed data? *Stat Med* 2008;27:3227–46.
30. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2013. URL <http://www.R-project.org/>.
31. Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nölle B, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. *Arthritis Rheum* 2000;43:1021–32. Erratum in: *Arthritis Rheum* 2000;43:2379.
32. Holle JU, Gross WL, Latza U, Nölle B, Ambrosch P, Heller M, et al. Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. *Arthritis Rheum* 2011;63:257–66.
33. Mukhtyar C, Flossmann O, Hellmich B, Bacon P, Cid M, Cohen-Tervaert JW, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism Systemic Vasculitis Task Force. *Ann Rheum Dis* 2008;67:1004–10.
34. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011;70:488–94.
35. Weidner S, Geuss S, Hafezi-Rachti S, Wonka A, Rupprecht HD. ANCA-associated vasculitis with renal involvement: an outcome analysis. *Nephrol Dial Transplant* 2004;19:1403–11.
36. Lane SE, Watts RA, Shepstone L, Scott DG. Primary systemic vasculitis: clinical features and mortality. *QJM* 2005;98:97–111.
37. Bourgarit A, Le Toumelin P, Pagnoux C, Cohen P, Mahr A, Le Guern V, et al. Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg–Strauss syndrome: a retrospective analysis of causes and factors predictive of mortality based on 595 patients. *Medicine (Baltimore)* 2005;84:323–30.

38. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P, et al. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine (Baltimore)* 2011;90:19–27.
39. Faurischou M, Westman K, Rasmussen N, de Groot K, Flossmann O, Höglund P, et al. Long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2012;64:3472–7.
40. Hogan SL, Falk RJ, Chin H, Cai J, Jennette CE, Jennette JC, Nachman PH. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med* 2005;143:621–31.
41. Pagnoux C, Hogan SL, Chin H, Jennette JC, Falk RJ, Guillevin L, et al. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. *Arthritis Rheum* 2008;58:2908–18.
42. Lionaki S, Blyth ER, Hogan SL, Hu Y, Senior BA, Jennette CE, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. *Arthritis Rheum* 2012;64:3452–62.
43. Walsh M, Flossmann O, Berden A, Westman K, Höglund P, Stegeman C, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2012;64:542–8.
44. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG for the Dutch Co-Trimoxazole Wegener Study Group. Trimethoprim–sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. *N Engl J Med* 1996;335:16–20.
45. Harper L, Morgan MD, Walsh M, Höglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis:



- long-term follow-up. *Ann Rheum Dis* 2012;71:955–60.
46. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013;369:417–27.
  47. Li ZY, Chang DY, Zhao MH, Chen M. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated vasculitis: a study of 439 cases in a single Chinese center. *Arthritis Rheumatol* 2014;66:1920–6.
  48. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007;18:2180–8.
  49. Walsh M, Merkel PA, Mahr A, Jayne D. Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis. *Arthritis Care Res (Hoboken)* 2010;62:1166–73.
  50. Springer J, Nutter B, Langford CA, Hoffman GS, Villa-Forte A. Granulomatosis with polyangiitis (Wegener's): impact of maintenance therapy duration. *Medicine (Baltimore)* 2014;93:82–90.
  51. De Joode AAE, Sanders JS, Cohen-Tervaert JW, Stegeman CA. Randomized clinical trial of extended versus standard azathioprine maintenance therapy in newly diagnosed PR3-ANCA positive vasculitis patients at high-risk for disease relapse. *Presse Med* 2013;42:680.
  52. Jayne D. Update on the European Vasculitis Study Group trials. *Curr Opin Rheumatol* 2001;13:48–55.
  53. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy. *N Engl J Med* 2014;371:1771–80.

**Table 1.** Clinical outcomes during long-term followup of WEGENT trial participants according to their initial randomization arm

Parameter	Azathioprine (n = 63)	Methotrexate (n = 63)	HR or aRR or aIRR [95% CI]	<i>P</i>
Months of therapy during trial, mean ± SD				
Maintenance	12.5 ± 7.3	11.5 ± 5.1		0.36
Glucocorticoids	27.0 ± 6.4	26.7 ± 7.8	–	0.86
Years of followup, median [95% CI]	11.9 [11.3–12.5]	12.0 [11.2–12.5]	–	0.81
Patients lost-to-followup*				
No.	8	6	–	0.57
Years of followup, median [range]	7.7 [4.9–9.8]	5.0 [2.7–9.7]	–	0.28
Deaths*, no. (%)	15 (23.8)	12 (19.0)	0.80† [0.37–1.71]	0.56
Patients with*				
≥1 relapses, no. (%; cases/100 person-years)	38 (60.3; 12.5)	34 (54.0; 9.8)	0.78‡ [0.13–4.85]	0.35
≥1 severe adverse events, no. (%; cases/100 person-years)	33 (52.4; 7.9)	35 (55.6; 8.3)	1.05‡ [0.70–1.58]	0.84
≥1 serious infections, no. (%; cases/100 person-years)	16 (25.8; 3.4)	22 (34.9; 4.8)	1.40‡ [0.20–9.80]	0.32
≥1 malignancies, no. (%; cases/100 person-years)	11 (17.7; 2.2)	10 (15.9; 1.9)	0.90‡ [0.56–1.47]	0.81
Patients with end-stage renal disease*, no. (%)	7 (11.0)	8 (12.7)	–	0.78
Relapse*				
No.	80	67	–	–
Mean no. (± SD) per patient	1.3 ± 1.4	1.0 ± 1.3	0.83§ [0.55–1.25]	0.38
Major, no.	58	51	–	–

Major, mean no. ( $\pm$ SD) per patient	0.9 $\pm$ 1.2	0.8 $\pm$ 0.9	0.81§ [0.53–1.26]	0.35
First only after stopping study maintenance drug, no. (%)	31/38 (81.6)	30/34 (88.2)	1.08 [0.89–1.31]	0.43
Relapse-free survival, median [95% CI], years	3.8 [2.4–5.5]	4.8 [3.7–8.4]		0.29
Major relapse-free survival, median [95% CI], years	5.0 [2.9–9.6]	6.3 [4.8–9.6]		0.46
Survival at 10-year followup*				
Overall (%) [95% CI]	75.1 [64.8–86.9]	79.9 [70.3–90.8]	0.80† [0.37–1.71]	0.56
Relapse-free (%) [95% CI]	26.3 [17.3–40.1]	33.5 [23.5–47.7]	0.80† [0.52–1.21]	0.29
Severe side effect-free (%) [95% CI]	43.6 [32.8–58.0]	42.1 [31.4–56.4]	1.02† [0.64–1.62]	0.94
Relapse- and severe side effect-free (%) [95% CI]	21.9 [13.7–35.1]	21.2 [13.1–34.4]	0.96† [0.65–1.43]	0.84
VDI per patient, mean $\pm$ SD	3.2 $\pm$ 2.5	3.1 $\pm$ 2.0	1.00§ [0.74–1.36]	1.00

\*Data censored at 10 years. HR = hazard ratio; aRR = adjusted relative risk on length of followup until the first event; aIRR = incidence risk ratio adjusted to length of followup.

**Table 2.** Multivariate analyses of factors associated with relapses or damage\*

Factor	Hazard ratio [95% CI]	<i>P</i>
Associated with relapses		
Anti-PR3ANCA (versus anti-MPOANCA or no ANCA)	1.99 [1.29–3.08]	0.002
Baseline serum creatinine†	0.99 [0.98–1.00]	<0.05
Glucocorticoid dose at the end of maintenance‡	1.05 [1.01–1.09]	0.01
Glucocorticoid duration§	1.03 [1.00–1.05]	0.02
Associated with VDI-assessed damage		
Age↑ (years)	1.05 [1.02–1.09]	0.002
Anti-PR3–ANCA (versus anti-MPO–ANCA or no ANCA)	2.53 [1.11–5.76]	<0.03
Baseline serum creatinine£	1.03 [1.00–1.05]	<0.02
Glucocorticoid dose at the end of maintenance¥	1.12 [1.01–1.24]	0.03

\*Data censored at 10 years.

†Each additional 10  $\mu\text{mol/liter}$  of creatinine at inclusion decreased the relapse risk by 1%.

‡Each additional mg of prednisone at the end of maintenance increased the relapse risk by 12%.

§Each additional 6 months of prednisone after stopping maintenance increased the relapse risk by 3%.

↑Each additional year increased VDI by 5%.

£Each additional 10  $\mu\text{mol/liter}$  of creatinine at inclusion increased the VDI by 3%.

¥Each additional mg of prednisone when AZA/MTX was discontinued increased VDI by 12%.

**Table 3.** Post-trial treatments prescribed during long-term followup

	AZA	MTX	
Therapy	n = 63	n = 63	<i>P</i>
<b>Cyclophosphamide</b>			
Patients, no.	26	24	0.77
IV induction therapies, no.	27	23	0.51
Oral induction therapies, no.	10	9	0.83
Oral cyclophosphamide after IV induction, no.	6	5	0.77
Cumulative dose, mean $\pm$ SD (g)	1.2 $\pm$ 2.7	1.0 $\pm$ 2.1	0.40
<b>Rituximab</b>			
Patients, no.	10	8	0.64
Induction therapies, no.	10	8	0.64
Remission-maintenance therapies, no.	6	6	0.98
Cumulative dose, mean $\pm$ SD (g)	11.9 $\pm$ 15.9	9.1 $\pm$ 11.3	0.67
GC $\geq$ 30 mg/day, no. patients	47	46	0.96
IVIg, no. patients	9	2	0.03
Plasma exchange, no. patients	1	0	1
Infliximab, no. patients	1	2	0.62

AZA = azathioprine; MTX = methotrexate; IV = intravenous; GC = glucocorticoids; IVIg = intravenous immunoglobulins.

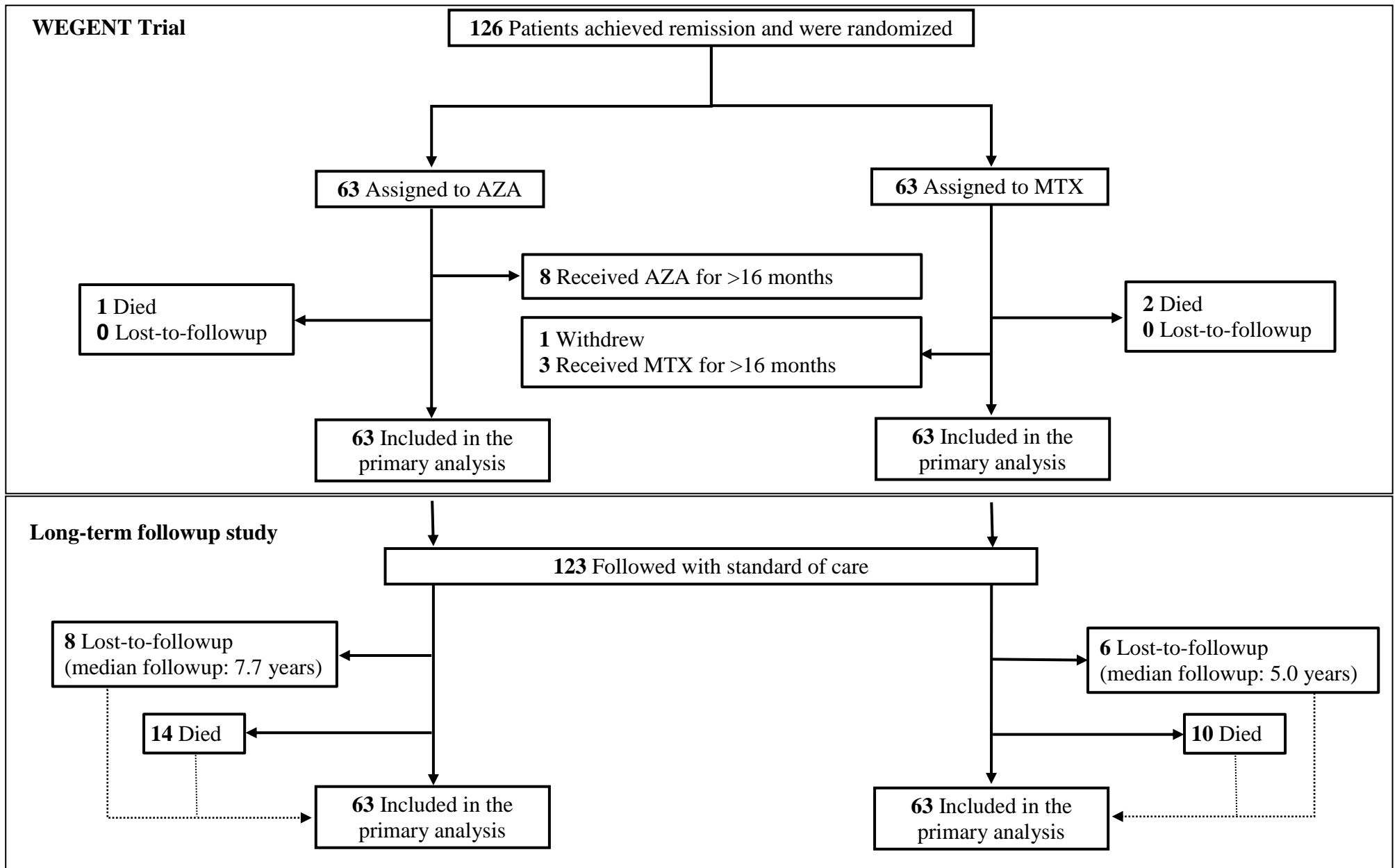
## FIGURE LEGENDS

**Figure 1.** Design of the WEGENT trial and of its long-term followup study. Followup was from trial inclusion to the last medical update or death. Patients were censored 10 years after inclusion. AZA = azathioprine; MTX = methotrexate.

**Figure 2.** Overall survival (A) censored at 10 years with confidence interval (---) and according to (B) randomization arm, (C) age or (D) vasculitis of the 126 enrolled patients in the WEGENT trial. AZA = azathioprine; MTX = methotrexate; MPA = microscopic polyangiitis; GPA = granulomatosis with polyangiitis (Wegener's). The vertical line indicates the discontinuation of azathioprine or methotrexate maintenance therapy after 1 year.

**Figure 3.** Relapse-free survival censored at 10 years according to (A) randomization arm and (B) ANCA status of the 126 enrolled patients in the WEGENT trial. AZA = azathioprine; MTX = methotrexate; ANCA status = anti-PR3 versus anti-MPO or none. The vertical line indicates the discontinuation of azathioprine or methotrexate maintenance therapy after 1 year.

Figure 1.



**Figure 2.**

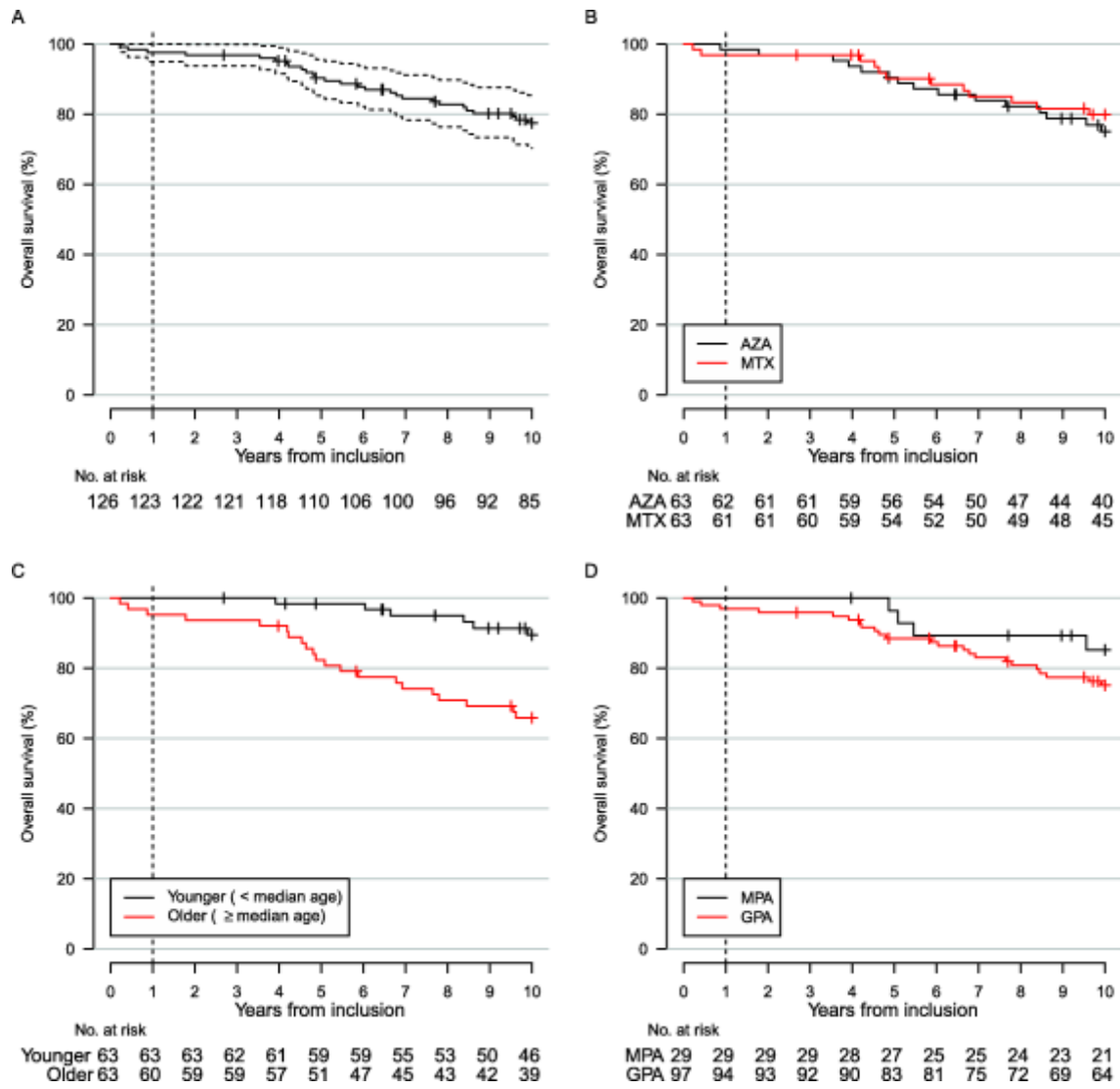




Figure 3.

