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TITLE

Low-dose Rivaroxaban plus Aspirin in Patients with Peripheral Artery Disease Undergoing Lower Extremity Revascularization with and without Concomitant Coronary Artery Disease: Insights from VOYAGER PAD

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ABSTRACT

Background

Patients with peripheral artery disease (PAD) are at heightened risk of both major adverse cardiovascular events (MACE) and major adverse limb events (MALE). Rivaroxaban 2.5 mg BID with aspirin versus aspirin alone reduced major adverse limb and cardiovascular events in PAD patients after lower extremity revascularization (LER) in the VOYAGER PAD trial. The concomitant presence and related risk of known coronary artery disease (CAD) in PAD patients is not well understood leading differences in adverse event risk between PAD patients. Therefore, efficacy and safety of rivaroxaban 2.5 mg BID in PAD patients with and without CAD after LER has not yet been described.

Methods

VOYAGER PAD randomized patient with PAD undergoing LER to rivaroxaban 2.5 mg twice daily plus aspirin versus aspirin alone. The primary endpoint was a composite of acute limb ischemia, major amputation of vascular cause, myocardial infarction, ischemic stroke, or cardiovascular death. The principal safety outcome was TIMI major bleeding. This is a pre-planned subgroup analysis investigating the contribution of concomitant CAD on efficacy and safety endpoints.

Results

Among 6,564 randomized patients, 2084 (32%) had CAD at baseline. In the placebo group, the 3-year Kaplan-Meier estimate of primary endpoint was 24.4% in those with concomitant PAD and CAD versus 17.9% in PAD only while MALE was 8.9% versus 10.2%, respectively.

Rivaroxaban decreased the rates of both MACE and MALE in each group particularly in those with concomitant PAD and CAD (HR 0.79, 95% CI 0.62-1.00) for MACE with a significant p-interaction of 0.03 considering MACE. The risk of bleeding was increased with rivaroxaban regardless of the presence of CAD.

Conclusions

In PAD patients underwent to LER, the presence of concomitant CAD leads to MACE events and confers an increased risk in PAD patients. Treatment with low-dose rivaroxaban and aspirin reduces the risk of MACE and MALE regardless of the presence of CAD; moreover, those with concomitant PAD and CAD derive a greater benefit with rivaroxaban in reducing MACE events versus those with PAD alone.

Key words: Peripheral Artery Disease, Coronary Artery Disease, Major Adverse Cardiovascular Event (MACE); Major Adverse Limb Events (MALE)

INTRODUCTION

Patients with peripheral artery disease (PAD) are at a heightened risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE).[1,2] PAD patients are often included as a single subgroup in cardiovascular (CV) outcome trials in patients with coronary artery disease (CAD) often defined by a known history, an abnormal ankle brachial index (ABI), or prior revascularization. Recent studies, however, suggest that there may be significant heterogeneity in risk profile among this broadly defined population. Patients with PAD and prior revascularization or amputation appear to be at heightened risk of MALE.[3,4,5] In contrast, patients with PAD and CAD (called polyvascular disease) appear to be at higher risk of MACE and to drive greater MACE reductions from antithrombotic therapies.[4,6] Although all patients with PAD have often been considered to have CAD based on the systemic nature of atherosclerosis, cohorts selected on the basis of PAD have been observed to have approximately 1/3 with known CAD.[7,8,9] These studies have generally defined the presence of CAD by a known history mostly including symptomatic disease including prior acute coronary syndrome. In these populations selected on the basis of PAD, the benefits of DAPT and more intensive P2Y12 inhibition have not show benefits, particularly for MACE where the benefits have been clear in CAD populations.[10,11,12] Similarly, the benefits of vorapaxar for MACE was heterogeneous with greater benefit in those with PAD and CAD versus those with PAD and no CAD.[4] Recently, patients enrolled in the Rivaroxaban with or without Aspirin in Patients with Stable Peripheral or Carotid Disease (COMPASS) trial demonstrated the benefit of combination of rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone for the reduction of MACE and cardiovascular death with consistent benefits in those with CAD or PAD.[13] This cohort, however, primarily had CAD (95% overall and 66% within the PAD subgroup) reflecting enrichment in enrollment for

polyvascular disease. The benefits of this regimen in PAD were confirmed in the VOYAGER PAD trial for a composite endpoint including irreversible harm events of the heart, limb and brain; however, in contrast to COMPASS, the benefits were driven primarily by limb events with fewer MACE events overall and less clear benefit for CV mortality. In VOYAGER PAD it was observed that 32% had known CAD, including only 11% who had prior acute coronary syndrome, significantly lower than that in COMPASS and consistent with other dedicated PAD trials. We therefore performed a pre-specified subgroup analysis from VOYAGER PAD to evaluate whether the risk profile for MACE and MALE events differed by the presence of known CAD at baseline. We then evaluated whether the benefits of rivaroxaban for MACE and for MALE were consistent regardless of concomitant CAD, including myocardial infarction subtypes. In addition, causes of death and the proportion attributable to acute coronary events was evaluated. Finally, the safety and benefit-risk of a rivaroxaban plus aspirin strategy was evaluated in those with and without CAD.

METHODS:

VOYAGER PAD (NCT02504216) is a Phase III, global, double-blind, placebo-controlled, endpoint driven trial of PAD patients undergoing LER randomized to rivaroxaban 2.5 mg twice daily or placebo on a background of aspirin 100 mg daily as previously described.[9,14] The protocol was designed and overseen by an academic executive committee, CPC Clinical Research (an Academic Research Organization) and the trial sponsors, Bayer and Janssen. The protocol was approved by the local Institutional Review Board (IRB), and informed consent was obtained from all study participants. The database is held by CPC Clinical Research, which independently has performed all data analyses for publication.

Study population

Enrolled study participants had symptomatic PAD defined by evidence of abnormal limb hemodynamics defined as an abnormal ankle-brachial index of ≤ 0.80 or toe-brachial index ≤ 0.60 with occlusive disease involving segments distal to the external iliac artery. Randomization occurred after a technically successful LER.[9,14] Patients were excluded who had a planned course of dual antiplatelet therapy greater than 6 months after the LER, need for systemic anticoagulation, recent acute limb or coronary ischemic events, impaired renal function at baseline (eGFR < 15mL/min/1.73m^2), and any documented history of intracranial hemorrhage. Known CAD was identified by investigators at baseline and included subjects with a prior myocardial infarction or coronary artery revascularization.

Concomitant therapies

Patients were prohibited from taking any additional antithrombotic therapy other than clopidogrel with study drug, including anticoagulants, higher doses of aspirin, vorapaxar, ticagrelor, or prasugrel. Following the revascularization, clopidogrel was allowed for up to 6 months at the discretion of the site investigator in combination with study drug and background aspirin.

Trial outcomes

The primary efficacy outcome was a composite of irreversible harm events consisting of ALI, major amputation of vascular causes, myocardial infarction (MI), ischemic stroke (IS), or CV death. The secondary efficacy outcomes were prespecified and tested in a hierarchical fashion in the following sequence: 1) the composite of ALI, major vascular amputation, MI, IS, or coronary heart disease death; 2) unplanned index limb revascularizations for recurrent limb ischemia; 3) vascular hospitalizations for a peripheral or coronary event of a thrombotic nature; 4) the composite of ALI, major vascular amputation, IS or MI or all-cause mortality; 5) the composite of ALI, major vascular amputation, MI, all-cause stroke or CV death; 6) all-cause mortality; and 7) venous thrombo-embolism. The principal safety outcome was TIMI major bleeding with ISTH major bleeding as a secondary bleeding outcome. An independent academic Clinical Adjudication Committee adjudicated all deaths, potential ischemic cardiovascular and limb adverse events, and all bleeding events in a blinded manner as previously published.[14] Source documents were collected for all deaths and cause was adjudicated by an independent blinded CEC using accepted CV trial conventions for those dying out of hospital. For this post-hoc

analysis, source documents were re-reviewed to provide further details regarding specific causes of deaths.

Statistical Analyses

The trial design has been previously published.[14] Distribution of continuous data was assessed with the Kolmogorov–Smirnov test. Normally distributed variables were expressed as mean ± standard deviation, whereas non-normal distributed ones were expressed as median and interquartile range. Categorical variables were reported as numbers and percentages. Continuous normally distributed variables were compared by using Wilcoxon test; differences between non-normally distributed variables were tested with the Mann-Whitney U test. Categorical variables were compared with chi-squared test, or Fisher exact test, when appropriate. Event probabilities are expressed as Kaplan-Meier estimates of the cumulative incidence at 3 years. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated with the use of a Cox proportional-hazards model. All reported p-values are two-sided and a P-value of <0.05 considered statistically significant. There was no adjustment for multiplicity. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

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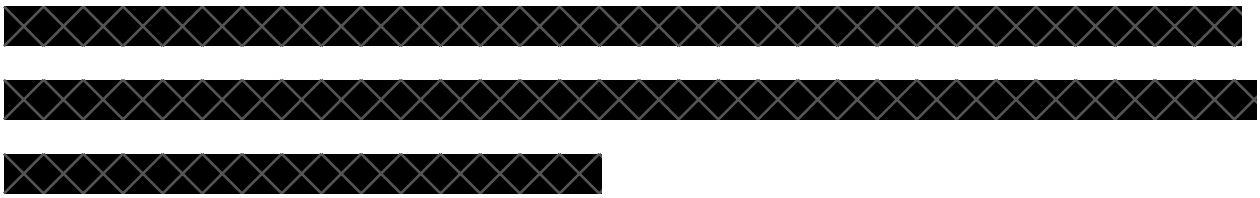


DISCUSSION

In this subgroup analysis, we analyzed the effect of concomitant CAD on CV and limb outcomes in PAD population after LER. In our study, patients with concomitant CAD and PAD shown an higher CV risk profile when compared with patients with PAD alone. The presence of concomitant CAD increased the risk of MACE events and its components as MI, IS and CV death but does not have a significant impact on the risk of MALE. Furthermore, rivaroxaban consistently mitigates the risk of MACE and MALE events regardless of the presence of concomitant CAD. As described in the original VOYAGER PAD study, the reduction of MALE with the presence of rivaroxaban was driven by a reduction in ALI seen in both subgroups. Finally, there was an increase in major bleeding after LER with the presence of rivaroxaban that was similar regardless of the presence of CAD.

Patients with symptomatic PAD undergoing LER have increased risk for MACE and MALE events. Previous research has recognized the heterogeneity of risk in PAD patients and CAD with polyvascular disease lead to MACE in those with PAD.[15] In VOYAGER PAD, we have identified that CAD increases the rates of MACE in those patients with symptomatic PAD requiring LER, including MI and CV death, consistent with previous evidences in PAD patients.[4,6] This is the only analyses to date that has been performed in a primary PAD population to demonstrate the effect CAD has on MACE risk within this PAD population and recent LER. Patients with symptomatic PAD have rarely been studied as the primary population in clinical studies. In recent CV outcome trials of antithrombotic and lipid-lowering agents, PAD was a subgroup of patients with symptomatic CV disease.[16,17,18] This creates the potential of effect modification of CAD on the PAD subgroup analyses. In the PAD subgroup analysis of the COMPASS trial, about two-thirds of patients had concomitant CAD. Both studies demonstrated

a robust response of rivaroxaban on MALE events, which in VOYAGER PAD, concomitant CAD did not have any effect modification. However, there was an increase rate of MI and CV death in our subgroup analyses in patients with PAD and CAD vs PAD alone likely representing effect modification of the presence of CAD. For example, the rate of MI in COMPASS was 3% compared to 8.7% in our study in PAD patients with concomitant CAD.[13] Despite the higher rates of MACE, there was still a robust benefit with rivaroxaban even in PAD with concomitant CAD in VOYAGER PAD trial.

Our results did demonstrate a significant interaction with the presence of concomitant CAD on the rate of MACE events. This represents effect modification from the presence of CAD. Our findings confirm the high heterogenicity in CAD prevalence in PAD patients and its impact on therapy and CV prognosis.[16] Rivaroxaban confirms the positive effect in MACE and MALE prevention in high risk population (i.e. CAD patients) aligned to other evidences in high risk subgroups from VOYAGER PAD trial as patient with chronic kidney disease or older patients where rivaroxaban reduced primary efficacy endpoint irrespective of eGFR class and age.[19,20] To further investigate, we analyzed the individual components of MACE as well as the composite of MI and IS. Rivaroxaban reduced MI and IS particularly in higher risk group as PAD with CAD with a real impact on prognosis.

Moreover, stratifying based on type of MI, we found a significant interaction. Specifically, a significant interaction is noted when looking at MI type 2. Type 2 MI's have a vast number of etiologies, but it is well-established that there is a significant thromboembolic component that contributes to the event regardless of the inciting systemic event.[21] Furthermore, prasugrel has previously been demonstrated to decrease the rate of Type II MI's, again supporting a significant thromboembolic component.[22] With the presence of concomitant PAD and CAD, rivaroxaban

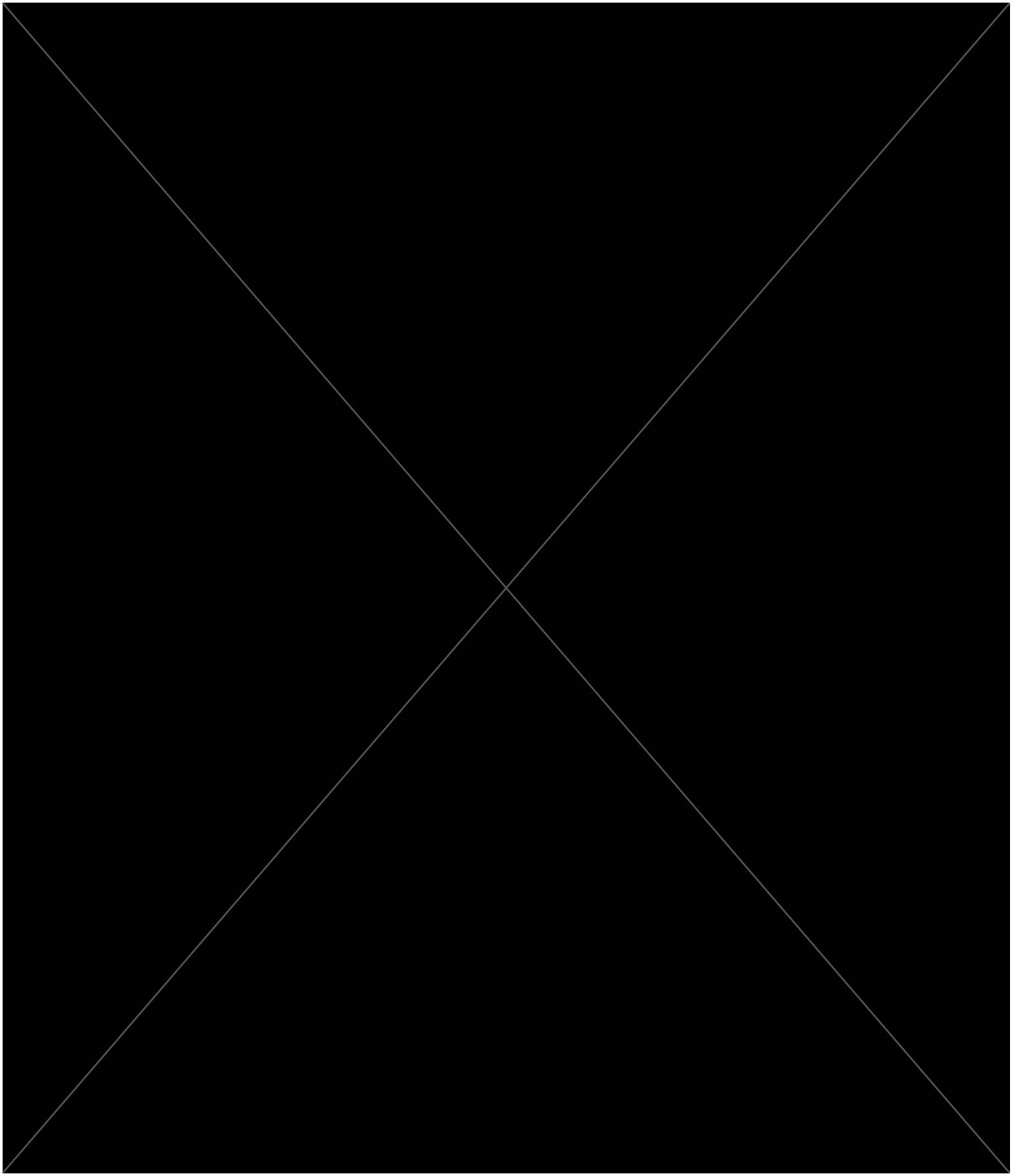
likely mitigates the thromboembolic component and associated plaque disruption of Type II MI's. Moreover, we analysed also causes of death in VOYAGER PAD. We highlighted high variability in causes of death in PAD patients contributing to heterogeneity and related challenge in PAD management. Patients recruited into trials for symptomatic PAD die of diverse causes. Atherothrombosis caused a minority of deaths, while heart failure, cancer, and infection are as or more frequent. These observations suggest that causes of death differ in populations selected on the basis of PAD versus CAD and that assumptions underlying categorization of deaths of unknown etiology should be carefully considered in these distinct populations. Our results are aligned to causes of death evidence from EUCLID trial where sudden cardiac death resulted in 20% while MI (5.2%) and IS (3.2%) were uncommon. In EUCLID, the most common causes of non-CV death were malignancies (17.9%) and infections (11.9%).[23]

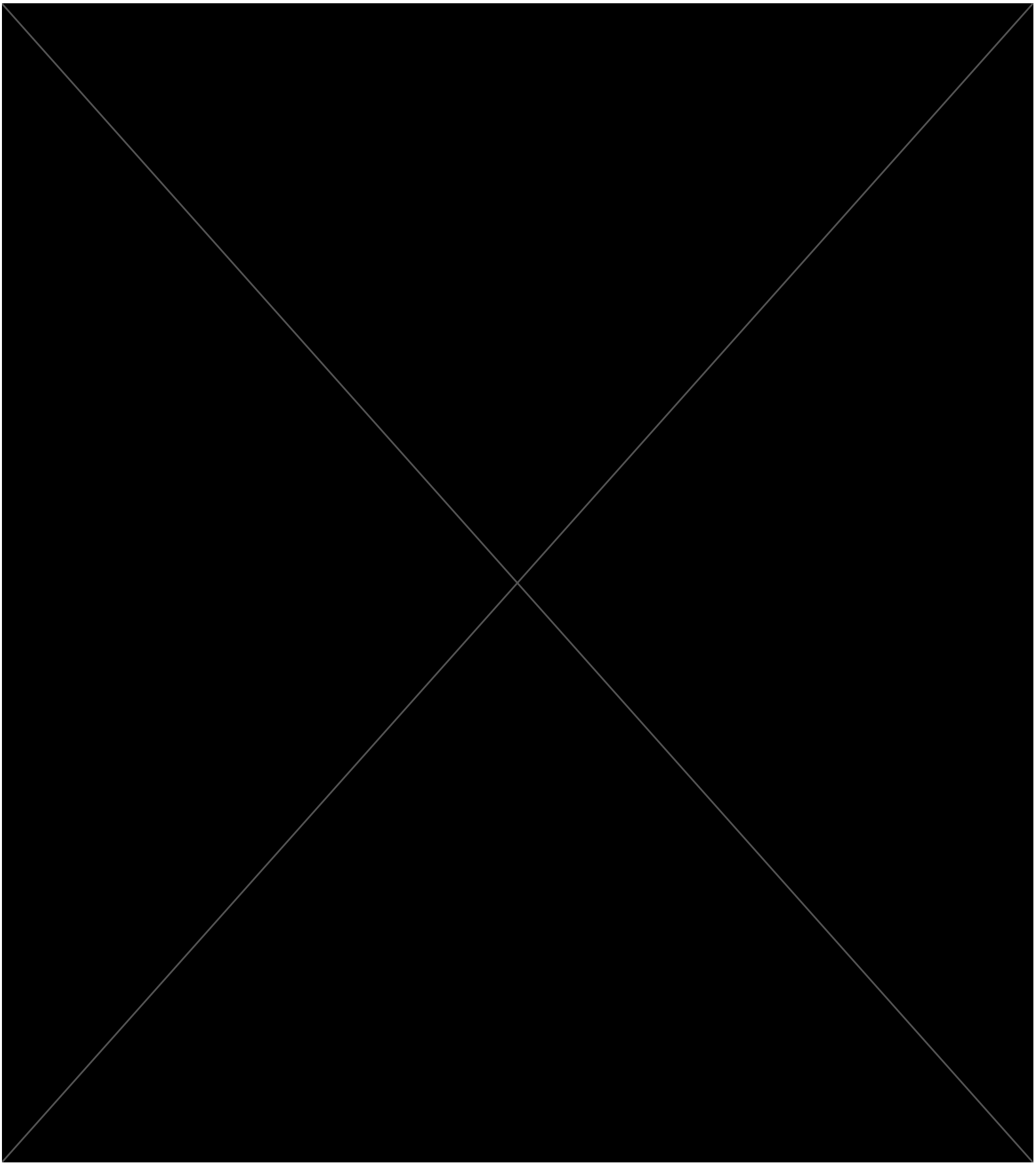
LIMITATIONS

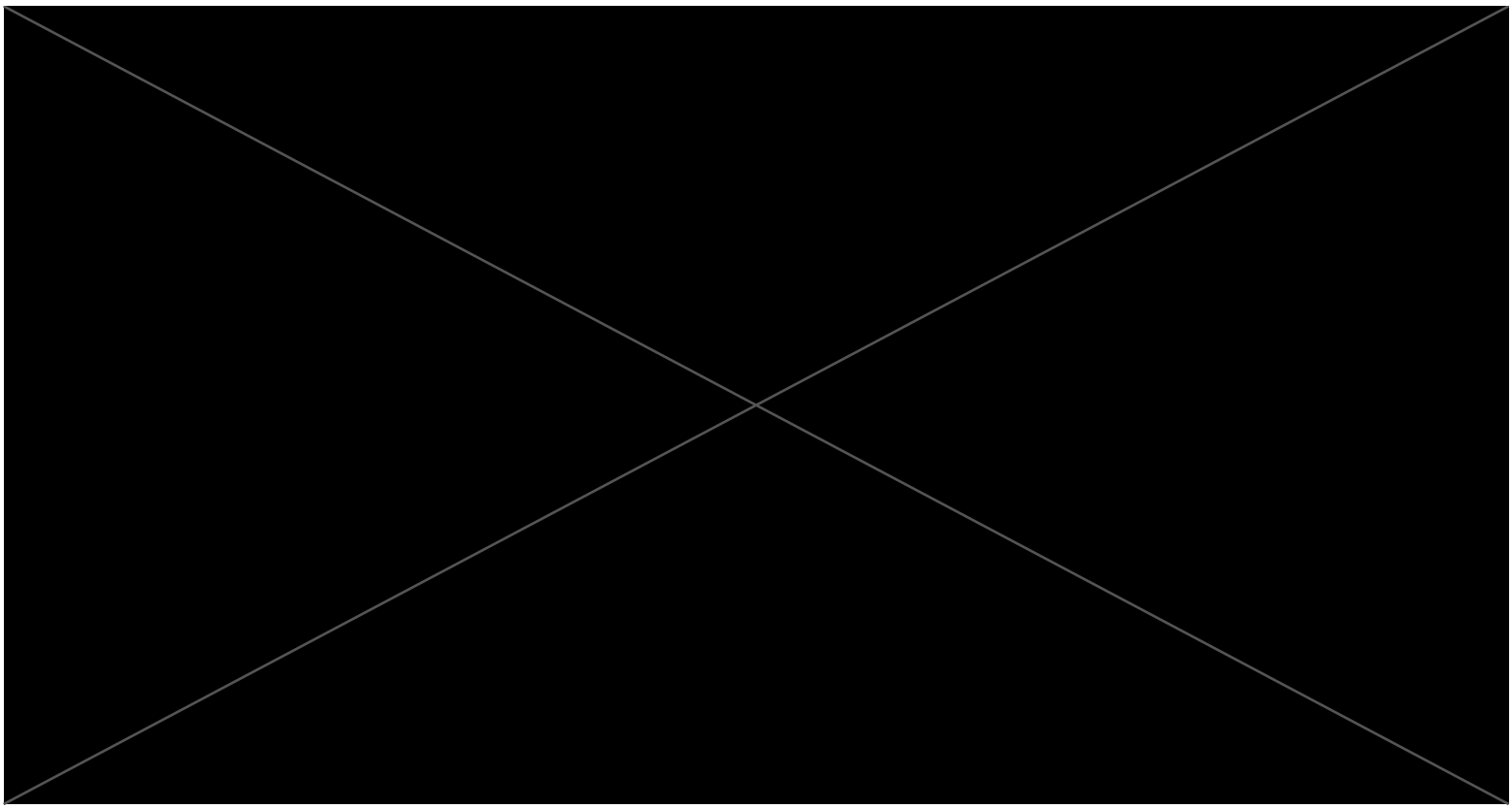
The results of this analyses should be interpreted in the context of the following limitations. This analysis was a planned subgroup analyses within a previously completed randomized controlled trial which leads to the potential of inadequate power to demonstrate significant differences between primary efficacy endpoints and safety signals. However, the subgroups analyzed were adequately powered to demonstrate effect modification of CAD on MACE and the pattern of safety events were consistent with the overall trial.

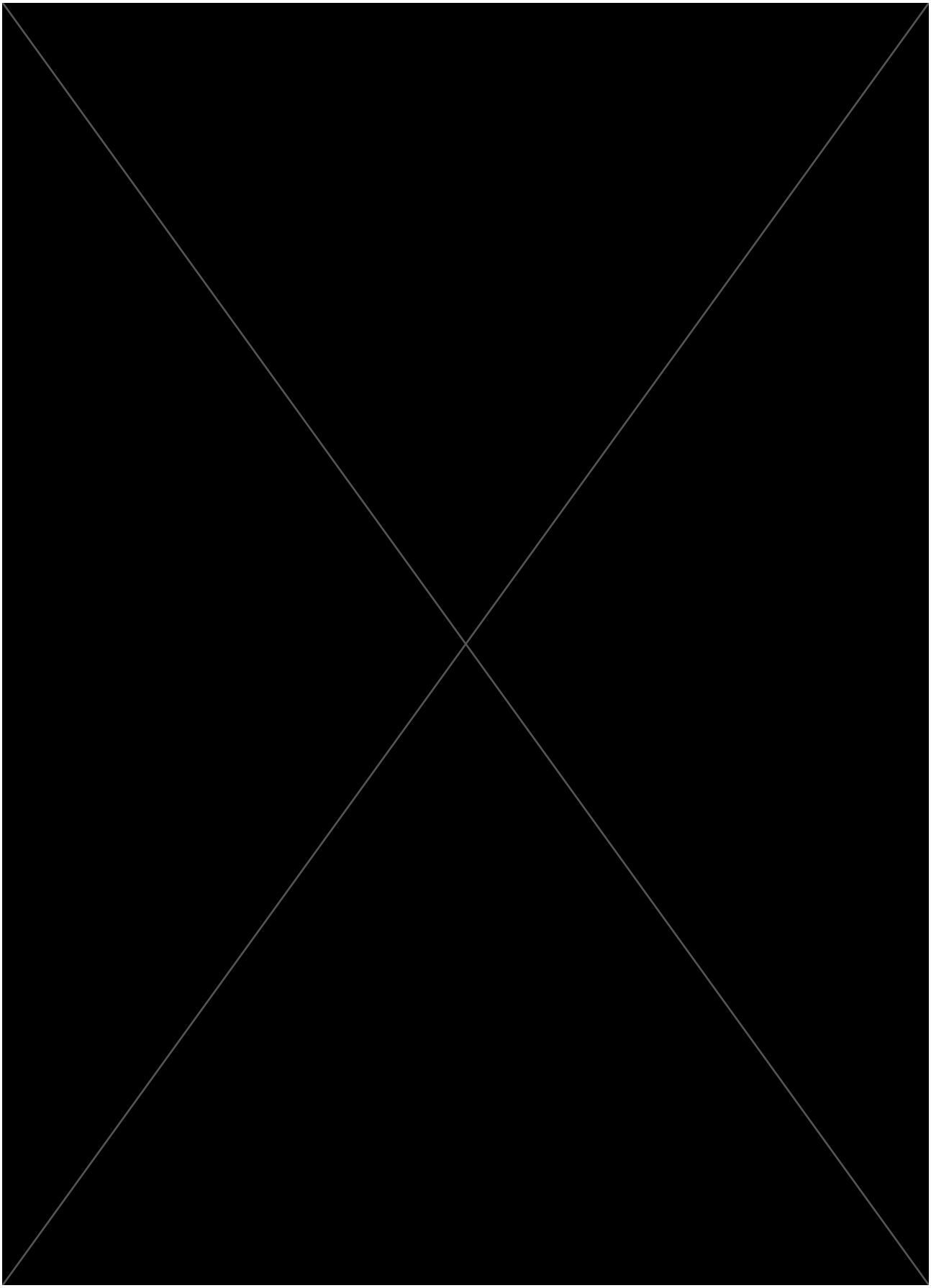
CONCLUSION

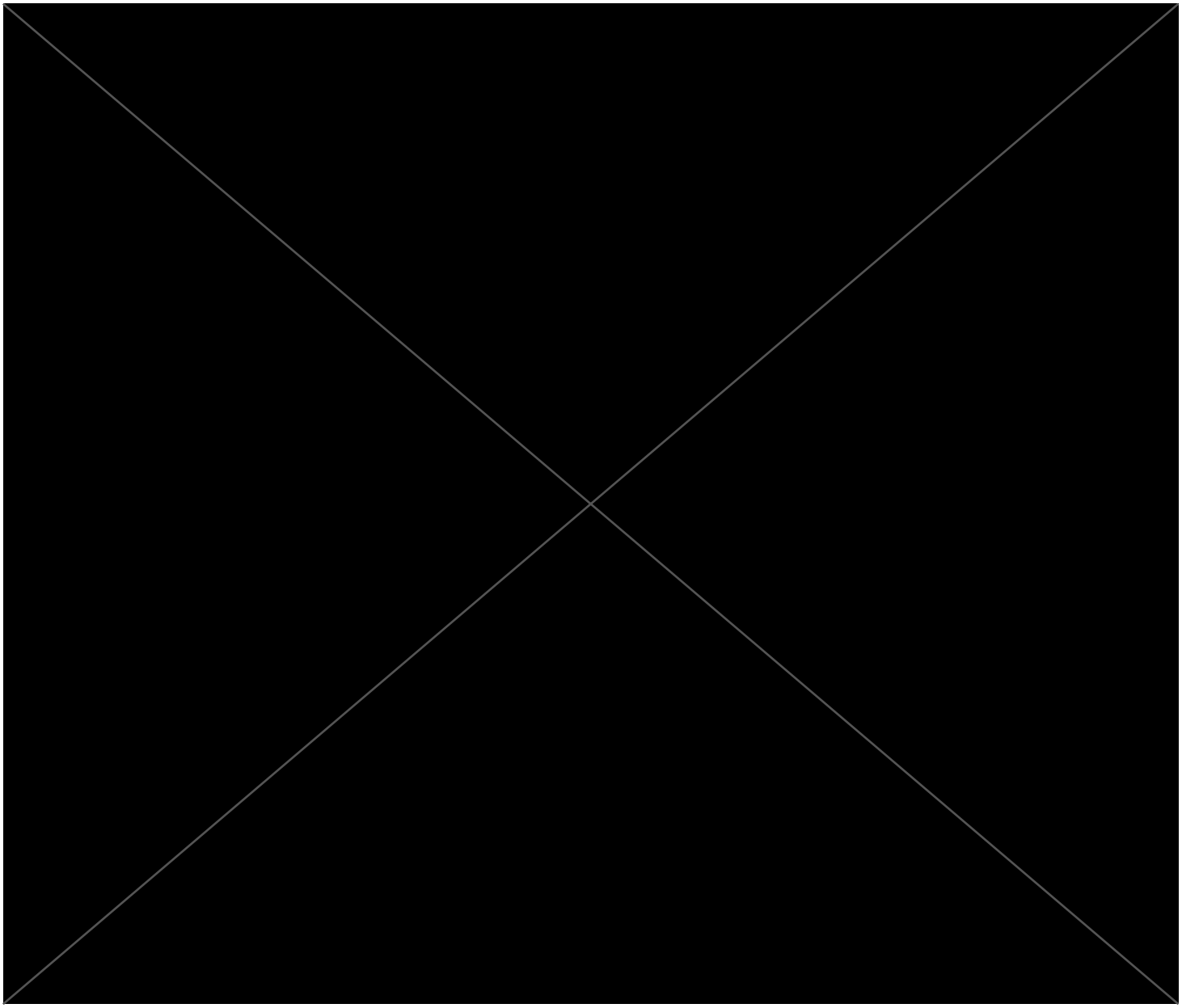
In this prespecified subgroup analyses of VOYAGER PAD, we have demonstrated that in patients with symptomatic PAD requiring LER with concomitant CAD, there is an increased rate of MACE with similar rates of MALE compared to those with PAD alone. Moreover, the presence of rivaroxaban 2.5 mg decreases the rates of MACE and MALE regardless of the presence of CAD. This is the first time this has been demonstrated in a primary PAD population. These data greatly support the use of rivaroxaban 2.5 mg in those patients with symptomatic PAD undergoing LER with concomitant CAD as they have a greater absolute benefit.

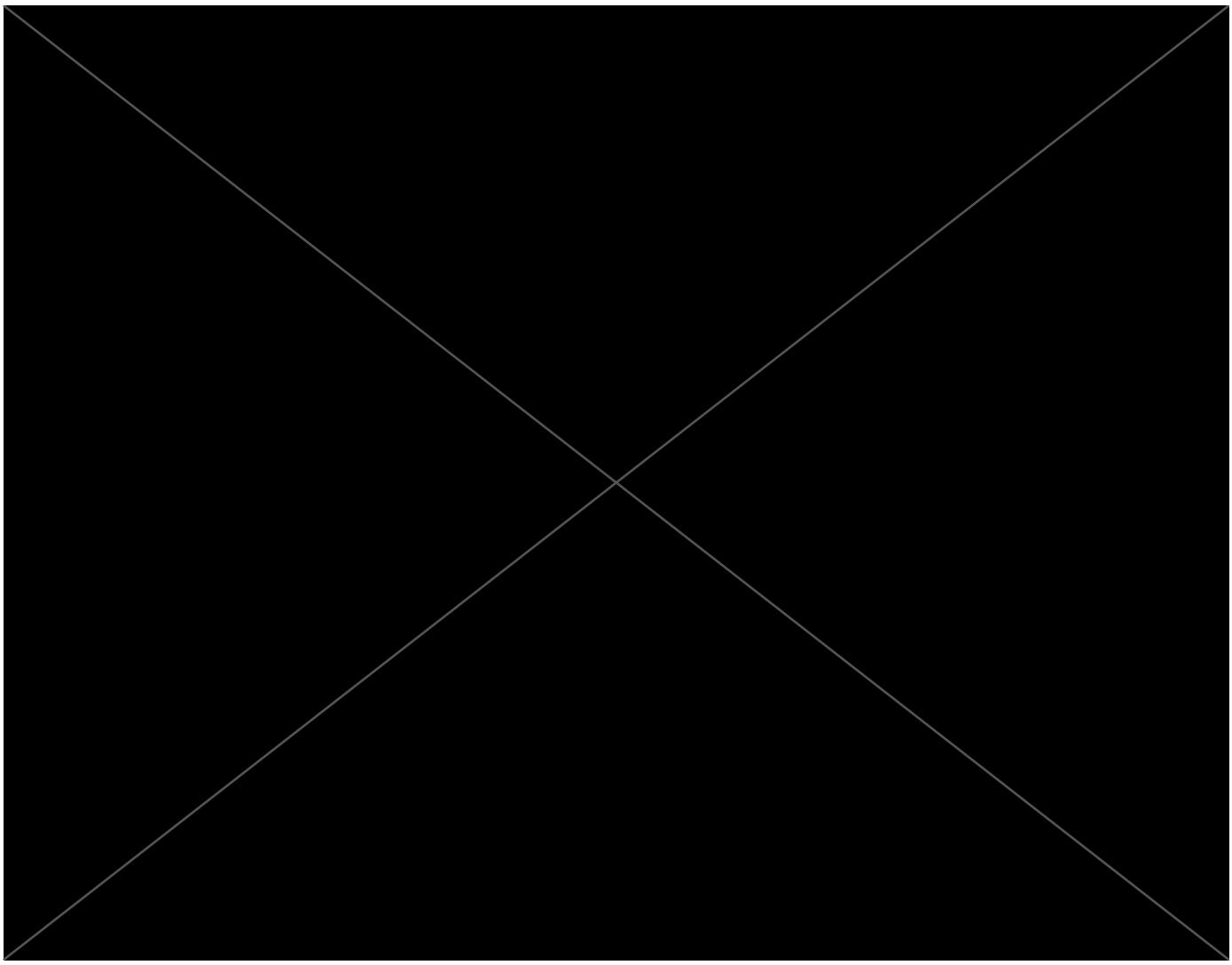


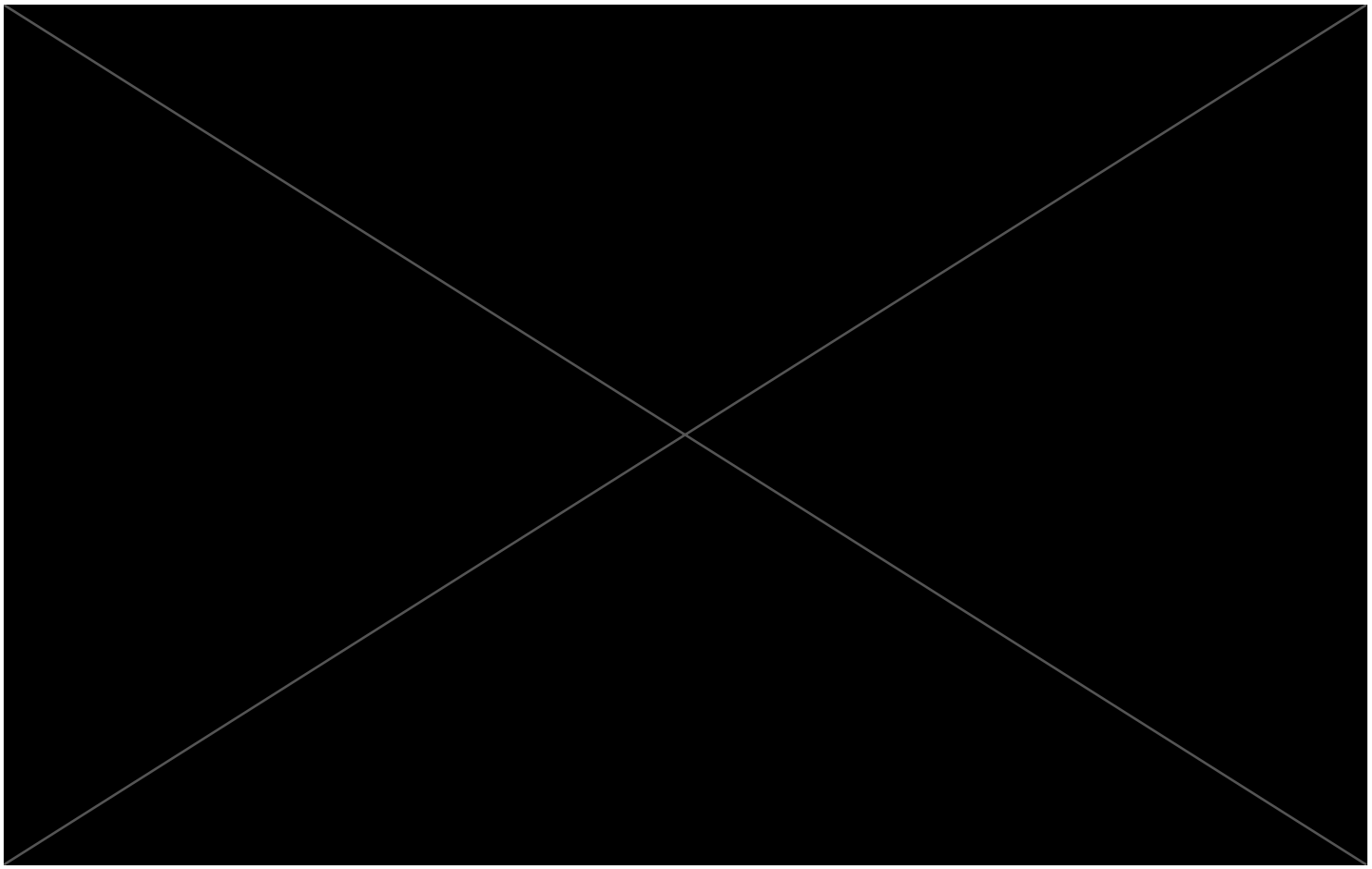


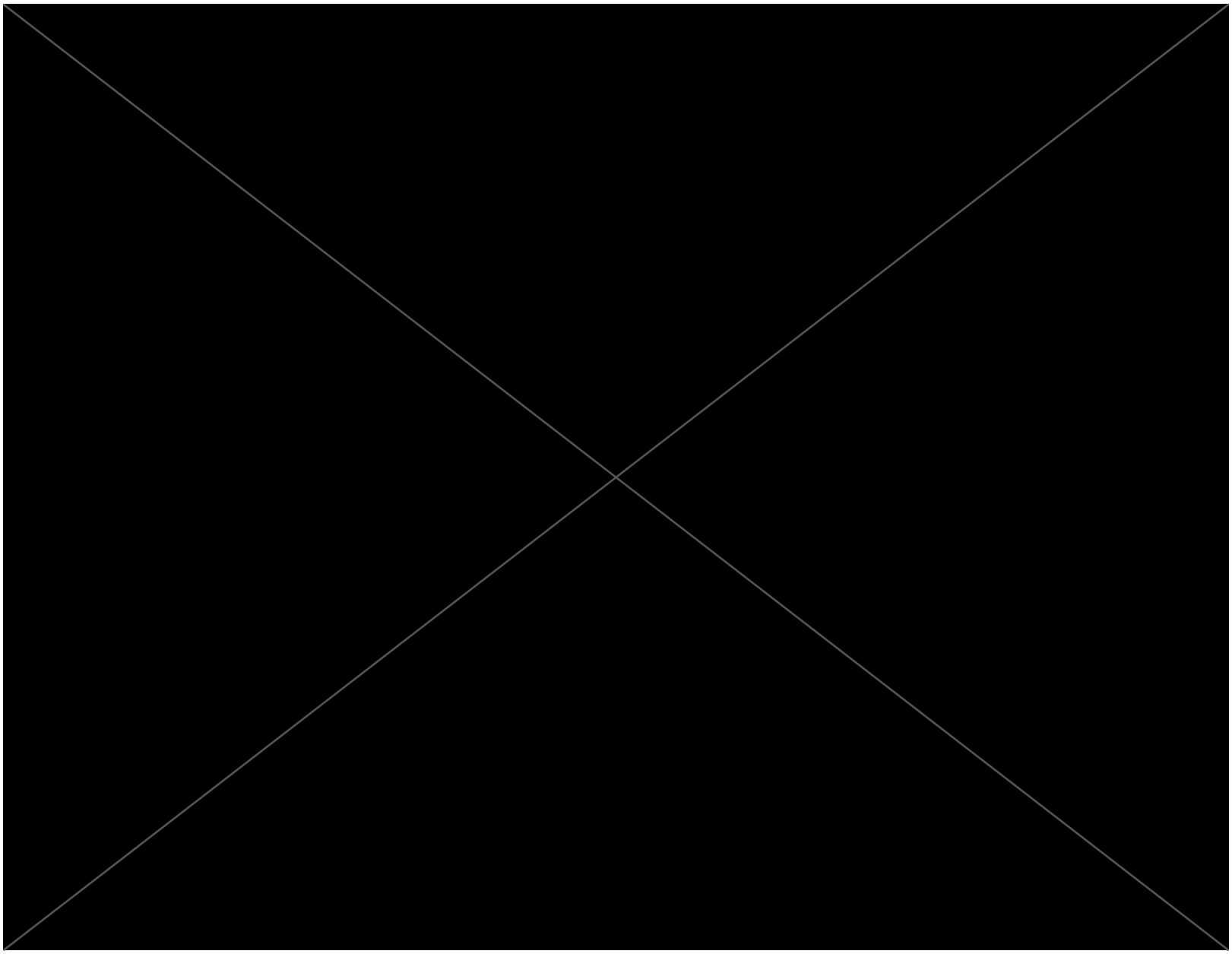


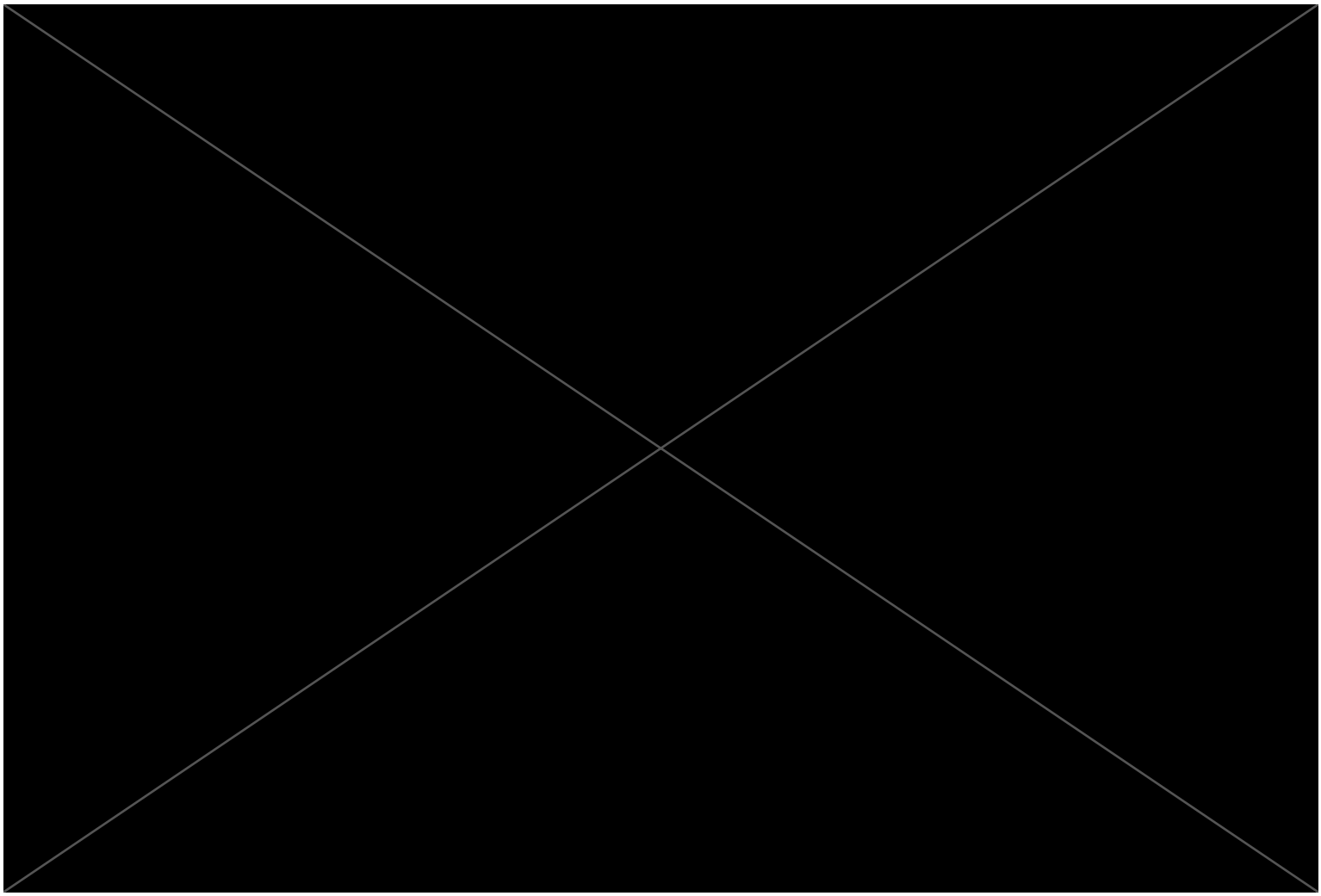


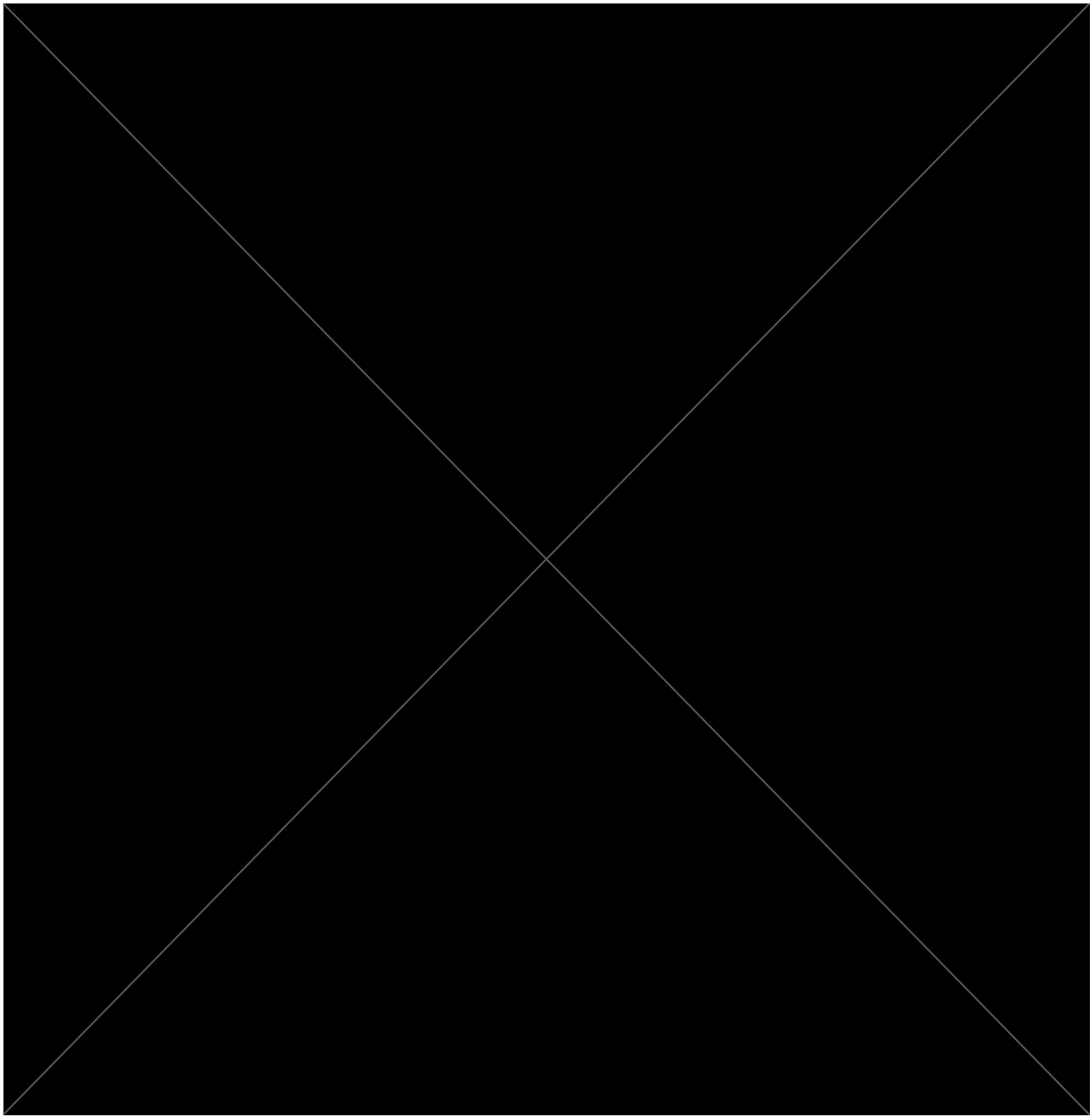


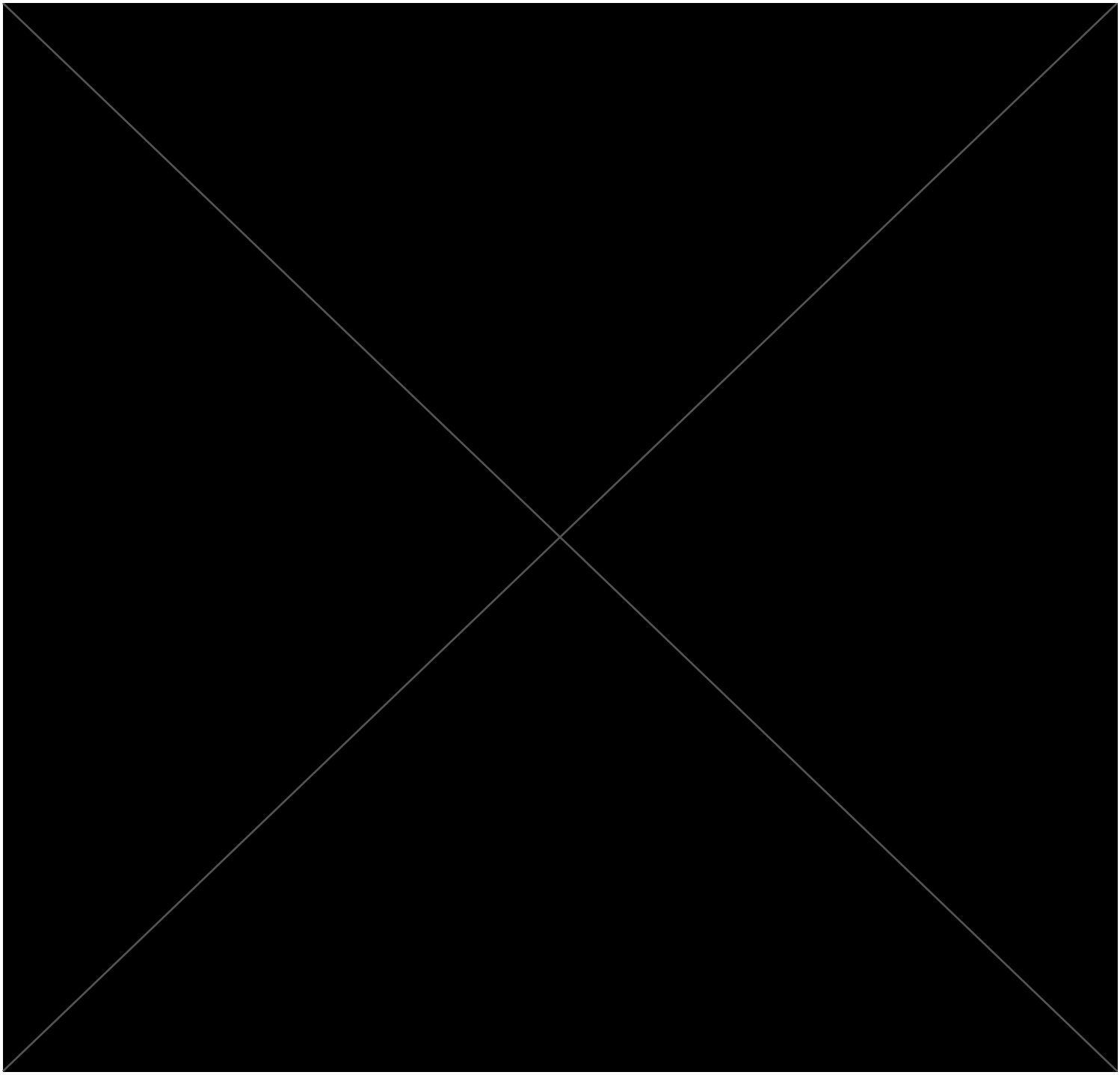


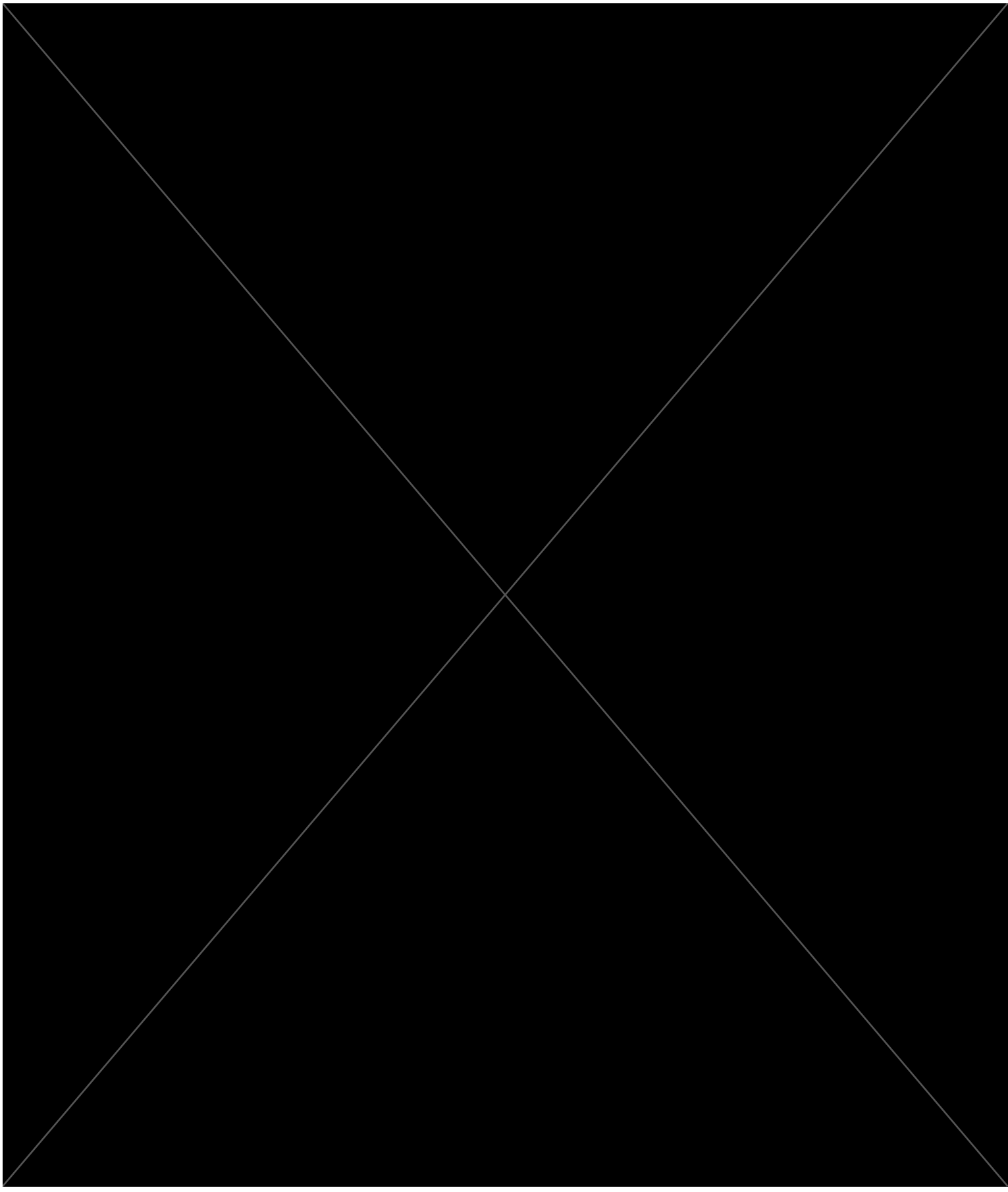












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