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Letter

Letter

Response by Yuk et al. to letter regarding article, "Association of menopausal hormone therapy with risk of cardiovascular disease in Korean women"

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We appreciate the thoughtful comments by Li et al. on our recent study, "Association of menopausal hormone therapy with risk of cardiovascular disease in Korean women".[1] Their insights highlight key areas for further exploration, and we welcome the opportunity to address their points.

Tibolone's mechanistic complexity and population-specific risks

Li et al. emphasized the need to explore genetic and metabolic factors underlying the association between tibolone and increased cardiovascular disease (CVD) risk (hazard ratio [HR], 1.38; 95% CI, 1.27-1.50).[2] We acknowledge the complexity of tibolone's tissue-selective activity. While our study highlighted tibolone's tissue-selective activity (eg, androgenic effects on lipid profiles), we did not have detailed data on genetic predispositions and insulin resistance in our analysis. As noted, tibolone exhibits estrogenic, progestogenic, and androgenic effects, which may influence its cardiovascular risk profile. While we briefly discussed potential mechanisms, such as increased C-reactive protein (CRP) levels and reductions in high-density lipoprotein cholesterol (HDL-C), we agree that further investigation is needed into genetic predispositions, metabolic factors, and the role of androgens in atherogenesis. Additionally, stratified analyses based on baseline cardiovascular risk factors, such as lipid profiles and inflammatory markers, could enhance risk prediction. Future studies incorporating biomarkers (eg, CRP and LDL/HDL ratios) and genetic data (eg, estrogen receptor polymorphisms) could further refine risk stratification among tibolone users, allowing for a more precise identification of high-risk subgroups and yielding additional clinical insights.

Dydrogesterone's cardioprotective potential in high-risk groups

The cardioprotective association of dydrogesterone (DYD) (HR, 0.74; 95% CI, 0.56-0.98) is indeed a compelling finding. As Li et al. pointed out,[2] DYD appears to differ from other progestogens in its vascular effects, and in-depth research is needed to determine whether its cardiovascular protective potential applies to women with metabolic comorbidities. Although prior research indicates a neutral or beneficial impact on endothelial function and hemostasis,[3] our study was limited by sample size and did not evaluate whether these benefits extend to women with preexisting metabolic conditions such as diabetes or dyslipidemia. We concur that prospective trials comparing DYD to other progestogens in high-risk populations could clarify its therapeutic role.

Menopausal hormone therapy duration and temporal risk patterns

Li et al. note the nonsignificant trend toward reduced CVD risk with prolonged menopausal hormone therapy (MHT) use (>6 years).[2] The interpretation of these findings in the context to the timing hypothesis is limited, as our data did not distinguish between women who had used MHT for more than 6 years immediately after menopause vs those who were more than 10 years postmenopausal.[4] Also, our median follow-up of 7.9 years precluded robust assessment of long-term effects. Extended follow-up studies are needed to determine whether this risk reduction reflects biological adaptation or is due to survivorship bias, such as treatment discontinuation due to early adverse events.

Cross-ethnic comparisons and regimen heterogeneity

Lastly, we appreciate the discussion on ethnic differences in MHT-related CVD risk. Our study focused on a Korean population, where tibolone use is more common than in Western cohorts. The *Women's Health Initiative* (WHI) study, which reported no significant increase in coronary heart disease risk with combined estrogen-progestin therapy, included a different

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demographic with distinct hormone regimens.[4] The WHI included older women (mean age 63), whereas 95% of our cohort were aged 40-59. Variations in body composition, dietary habits, and genetic factors (eg, CYP3A4 metabolism of tibolone) may further influence cardiovascular risk profiles. We agree that cross-ethnic comparisons are essential to understanding the role of genetic, dietary, and environmental factors in modulating MHT effects. Future research should incorporate more diverse populations to improve the generalizability of findings.

Conclusion

We appreciate the insightful observations by Li et al. and recognize the need for further research to elucidate regimen-specific and population-specific cardiovascular implications of MHT. Their comments reinforce the importance of individualized therapy and highlight key directions for future studies.

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Conflict of interest: None declared. This response adheres to academic rigor while diplomatically addressing methodological limitations and fostering collaborative next steps.

Authors' contributions

Jin-Sung Yuk (Formal analysis [lead], Investigation [lead], Methodology [lead], Project administration [lead], Visualization [lead], Writing—original draft [equal]), Gwang Sil Kim (Data curation [equal], Funding acquisition [lead], Resources [equal]), Dong-Gil Kim (Resources [equal]), Young Sup Byun (Resources [equal], Software [equal]), Myoung-Hwan Kim (Resources [equal]), Sang-Hee Yoon (Resources [equal]), Gwan Hee Han (Resources [equal]), and Byung Gyu Kim (Conceptualization [lead], Investigation [equal], Supervision [lead], Validation [lead], Writing—original draft [lead], Writing—review & editing [lead])

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