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Low-Dose Aspirin Chemoprevention in Lynch Syndrome

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This summary reviews Burn J, Borthwick GM, Elliott F, et al. Aspirin for cancer prevention in individuals with Lynch syndrome: first results from the CaPP3 multicentre, randomised, double-blind, non-inferiority trial. Lancet Gastroenterol Hepatol 2026;11(9):760-774.

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COLON

STRUCTURED ABSTRACT

Question: In individuals with Lynch syndrome, is daily aspirin at 100 mg or 300 mg daily non-inferior to 600mg daily for the prevention of Lynch-syndrome associated cancers?

Design: The Cancer Prevention Programme 3 (CaPP3) trial was a multicenter, parallel-group, randomized, double-blind, dose non-inferiority trial.

Setting: The patients for the trial were from clinical genetics centers in the United Kingdom, Australia, Finland, Israel, and Spain.

Patients: Eligible participants included adults (≥18 years) with confirmed Lynch syndrome who carry a pathogenic variant in *MLH1*, *MSH2*, *MSH6*, or *PMS2*, whether newly diagnosed or undergoing routine cancer surveillance. Key exclusion criteria were regular, long-term nonsteroidal anti-inflammatory drug use, aspirin intolerance or sensitivity, active bleeding disorders, or other clinically significant medical illnesses.

Intervention: Participants were randomly assigned (3:3:4 ratio) to receive a daily dose of 100 mg, 300 mg, or 600 mg aspirin for a 2-year double-blind treatment phase. Following this, participants transitioned to an open-label phase of 100 mg daily via hospital prescription (75 mg in the UK due to local availability). While intervention discontinuation was permitted at any time, adherence to the 5-year treatment course was encouraged.

Outcomes: The primary outcome was the number of new mismatch-repair deficient (Lynch syndrome-associated) cancers diagnosed following intervention initiation. Secondary outcomes included the number and cumulative incidence of colorectal cancer, cancer of any organ, and 2-year blinded safety outcomes (specifically tracking adverse events such as gastrointestinal effects, bleeding, allergy, fever, hearing disturbances, and laboratory abnormalities).

Data Analysis: The primary analysis evaluated whether lower daily aspirin doses (100 mg and 300 mg) were non-inferior to 600 mg daily for cancer prevention in Lynch syndrome, determined by 2 complementary approaches: time to first cancer and overall cancer burden. Cox proportional hazards regression and Kaplan-Meier curves were used to estimate age- and sex-adjusted hazard ratios (HRs) for time to first cancer, while negative binomial regression estimated age-, sex-, and location-adjusted incidence rate ratios (IRRs) to capture overall cancer burden. Non-inferiority was declared for a lower dose if the upper bound of the 95% confidence interval for both the HR and IRR remained below 1.5 for both intention-to-treat (ITT) and per-protocol (PP) analyses.

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Results: The ITT population consisted of 1,866 patients, and the PP population consisted of 1,136 patients who adhered through the blinded phase and consented to continue into the open-label phase at the 2-year review.

For the primary endpoint, the 300 mg aspirin group did not demonstrate non-inferiority compared to 600 mg for either time to first cancer (HR) or overall cancer burden (IRR) in both the ITT and PP populations. The 100 mg aspirin group demonstrated non-inferiority in the ITT analyses for both HR and IRR, but only for cancer burden (IRR) in the PP analysis **(Table 1).**

For the secondary endpoints, the 300 mg aspirin group failed to demonstrate non-inferiority for any outcome in either the ITT or PP analyses. For the 100 mg group, colorectal cancer burden (ITT IRR 0.85 [95% CI 0.48-1.48]) and overall cancer burden (ITT IRR 0.97 [95% CI 0.69-1.36]; PP 0.94 [95% CI 0.62-1.44]) met criteria for non-inferiority, but time to first colorectal cancer or time to first

cancer did not meet this threshold. Safety outcomes generally favored the lower aspirin dose. Although there was a numerical increase in serious adverse events with increasing aspirin dose (4.6% with 100 mg vs 6.3% with 600 mg), this was not statistically significant ($P = 0.19$). In contrast, serious bleeding events demonstrated a significant dose-response relationship, occurring in 0% of participants receiving 100 mg compared with 1.5% receiving 600 mg over 5 years ($P = 0.004$), suggesting that the principal safety concern with higher-dose aspirin is bleeding rather than an increase in serious adverse events overall.

Comparison	ITT HR (95% CI)	ITT IRR (95% CI)	PP HR (95% CI)	PP IRR (95% CI)
100 mg vs 600 mg	0.97 (0.67-1.42) ✓	0.94 (0.65-1.38)✓	1.00 (0.61-1.63)×	0.90 (0.55-1.46) ✓
300 mg vs 600 mg	1.28 (0.91-1.80) ×	1.12 (0.79-1.61)×	1.42 (0.91-2.19)×	1.28 (0.82-1.98)×

Table 1. Primary endpoint of new primary Lynch syndrome (MMR-deficient) cancers, analyzed 2 ways: time-to-first-cancer (Cox HR) and cancer burden across multiple anatomical sites (negative binomial regression IRR).

✓ = non-inferiority met

× = non-inferiority not met

CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratios; ITT, intention to treat; MMR, mismatch repair; PP, per-protocol.

COMMENTARY

Why Is This Important?

The CaPP3 trial is the long-awaited follow-up to the landmark CaPP2 trial,[1] which established aspirin as an effective chemopreventive agent in Lynch syndrome. In CaPP2, participants randomized to 600 mg of aspirin daily experienced a significantly lower risk of colorectal cancer than those receiving placebo (HR 0.65, 95% CI 0.43-0.97; $P = 0.035$). While CaPP2 demonstrated the efficacy of aspirin in reducing cancer risk, adoption of the 600 mg dose has been limited by concerns regarding bleeding risk and long-term tolerability. For example, a 2017 survey of general practitioners found that only 62% were willing to prescribe 600 mg daily, compared with 91% who would prescribe 100 mg.[2]

Although CaPP3 did not formally demonstrate non-inferiority of either 100 mg or 300 mg aspirin compared with 600 mg, potentially due to suboptimal follow-up duration up to 8 years, the overall findings are very encouraging.

As demonstrated in the study, both 600 mg and 300 mg (typically 325 mg) doses of aspirin can cause side effects such as bleeding and gastrointestinal discomfort. In our experience, patients largely tolerate "baby" aspirin (81 mg in the United States rather than 100 mg) very well, particularly in younger individuals who are otherwise healthy.

Key Study Findings

Although the 100 mg aspirin dose did not formally meet criteria for non-inferiority, effect estimates were similar to higher doses. Given the favorable adverse effect profile of low-dose aspirin, an 100 mg (or 81 mg) dose of aspirin is a reasonable option for cancer prophylaxis in Lynch syndrome patients.

Caution

Although the study results did not meet non-inferiority thresholds, the median follow-up of 5.5 years was relatively short compared to the 20+ year follow-up of CAPP2. Subsequent follow-up studies could potentially narrow confidence intervals below the non-inferiority threshold if there truly is no significant difference in efficacy with lower aspirin doses.

It is also important to note that this study may not address the role of low-dose aspirin in *PMS2* Lynch syndrome patients or obese patients. *PMS2* Lynch syndrome patients were under-represented in CAPP3, as it has been historically in other large-scale studies.[3] CAPP3 was also under-powered to account for obesity, which is important because individuals with obesity may require higher aspirin doses.[4]

Our Practice

In our practice, we routinely discuss aspirin chemoprevention with individuals with Lynch syndrome, although this is not a one-size-fits-all recommendation. Low-dose 81 mg aspirin daily is a reasonable choice for those prone to peptic ulcer disease or bleeding. This increased bleeding risk can be seen not only in those with other medical comorbidities, but also young, otherwise healthy Lynch syndrome patients who engage in contact sports.[5] In addition, the chemopreventive benefit of aspirin may not emerge for 5-10 years after initiation. Therefore, we are less likely to initiate aspirin in adults age 70 and up whose risk of bleeding often outweighs any delayed cancer preventative benefit that they would receive at that age.[1] We also counsel patients that the demonstrated benefit of aspirin depends on consistent long-term use, and that aspirin should be viewed as an adjunct to guidelines based surveillance colonoscopy.[6] For example, in this study 5%-10% of participants still developed colorectal cancer over a relatively short time frame regardless of aspirin dose.

For Future Research

In addition to longer follow-up of the CaPP3 cohort to refine non-inferiority analyses of lower aspirin dosages, future

studies should investigate the impact of aspirin in the context of other risk-modifiers such as obesity, prior cancer history, and colonoscopy (or other risk-reduction modalities). Finally, the role of aspirin in cancer chemoprevention may also change depending on the results of ongoing vaccine trials against Lynch-syndrome associated cancers.[7]

Conflict of Interest

The authors of the summary declare no conflicts of interest.

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