Trials

STUDY PROTOCOL

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Effectiveness of long-term low-dose aspirin in the prevention of gastric cancer after *Helicobacter pylori* eradication: study design and rationale of Ardabil gastric cancer randomized placebo-controlled prevention trial (AGCPT)

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Abstract

Background In addition to *Helicobacter pylori* (*H. pylori*) infection eradication, some medications, including aspirin, metformin, and statins, have been suggested to have protective effects against gastric cancer (GC) development in observational studies. We launched the Ardabil gastric cancer randomized placebo-controlled prevention trial (AGCPT) to evaluate the effectiveness of long-term low-dose aspirin use for the prevention of development and mortality of GC after *H. pylori* eradication.

Methods/design AGCPT is a prospective population-based double-blind, randomized clinical trial. The study sample was targeted at 21,000 participants aged from 35 to 70 years old, both sexes, in Ardabil, a province in northwest Iran with relatively high rates of GC incidence and mortality. All eligible participants were initially tested for *H. pylori* infection using a *H. pylori* stool antigen test. Participants with positive tests undergo *H. pylori* eradication by standard treatment regimens. All participants with a negative test and those with a positive test with a subsequent confirmed *H. pylori* eradication test were entered into the intervention phase. In the intervention phase, participants were allocated randomly into either the treatment (daily oral consumption of 81 mg enteric-coated aspirin tablets) arm or the control (placebo) arm using permuted balanced blocks. Subjects will be followed for an average period of 10 years to evaluate the incidence and mortality rates of GC.

Discussion In addition to preventing other diseases like cardiovascular events, aspirin may prevent GC incidence and mortality. AGCPT will investigate the difference between the two study arms in the proportion of the cumulative

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incidence and mortality rates of GC. The study's results may help policymakers and researchers update the strategies for GC prevention.

Trial registration This trial with the registry name of "The effect of Low-dose Aspirin in the Prevention of Gastric Cancer" was registered in the Iranian Registry of Clinical Trials, IRCT.ir, under the identifier IRCT201105082032N3. Registered on April 21, 2017.

Keywords Aspirin, Gastric cancer, Prevention, Randomized controlled trial

Introduction

Gastric cancer (GC) ranks the fifth most diagnosed cancer and the fourth leading cause of cancer-specific deaths globally [1]. According to the estimates from GLOBOCAN 2020, about 1.09 million new GC cases and 769,000 GC-related deaths occur worldwide each year [1]. There is an evident diversity in the geographical pattern of GC incidence and mortality rates across populations [2]. Iran is also a hotspot for GC [3]. Based on the reported results from the Iranian National Population-based Cancer Registry, GC is the most common neoplasm in men and the third in women and also the leading reason for cancer-related mortality in the whole population [4]. In Iran, the age-standardized incidence rate varies from 50 per 100,000 population in the northwest (Ardabil) to 7 in the south (Hormozgan) [4, 5].

There is evidence from epidemiologic, basic, and clinical research that *Helicobacter pylori* (*H. pylori*) is the most important etiology of GC. Approximately 90% of non-cardia GC cancers are attributable to *H. pylori* infection [6]. Several studies have already shown that *H. pylori* eradication reduces the risk of gastric cancer development. However, up to 50% of individuals progress to gastric cancer even after successfully eradicating *H. pylori* infection [6–8]. In addition to *H. pylori* eradication, a few other medications, including aspirin, metformin, and statins, have been suggested to have protective effects against GC, especially after *H. pylori* eradication [9]. In recent decades, several meta-analyses based on epidemiologic studies have unanimously confirmed that long-term low-dose aspirin intake may reduce the incidence and mortality rates of GC. However, the underlying mechanisms needed to be fully and thoroughly understood [10–19]. The current literature about the attributable preventive effect of aspirin on GC is mainly limited to observational studies rather than clinical trials, which may be biased or have unmeasured confounding factors. Moreover, we should be aware of gastrointestinal complications in prolonged regular aspirin use alone. This fact warrants a large-scale randomized control trial (RCT), particularly in a high-incidence population of GC like Northwestern Iran, in which safety can also be closely monitored. To the best of our knowledge, this study will be the first of its kind, and its results can be used as a model in GC chemoprevention at both national and global levels.

Objectives

The Ardabil gastric cancer prevention trial (AGCPT) is a prospective double-blind placebo-controlled randomized clinical trial to evaluate the effectiveness of long-term low-dose aspirin use for prevention in the incident and mortality of GC after *H. pylori* eradication. The primary objective of the AGCPT study is to determine the cumulative incidence rate of GC 5 years after the end of treatment. Secondary outcomes of interest include the incidence rate of precancerous gastric lesions, any adverse events or drug-related side effects, and any risk or protective factors associated with GC.

Methods/design

Trial design

AGCPT is a population-based, double-blind, parallel-group, phase III, placebo-controlled, two-arm randomized controlled trial. We targeted to include 21,000 adult participants in the study.

Participants, interventions, and outcomes

Study setting

Ardabil Digestive Disease Research Center (DDRC) was the recruitment and data collection location. Participants were randomly invited to DDRC and recruited if eligible. Ardabil is a northwestern province of Iran with the highest incidence rate of GC and a high prevalence rate of *H. pylori* in the country [4, 20]. Moreover; DDRI will manage the conduction of the study.

A pilot study on 1000 individuals (500 in each group) was conducted to evaluate the current trial's logistics and answer the following questions: feasibility and adherence rate, validity and reliability of methods, the amount of aspirin consumption in the general population, and the participation rate. The pilot study's results will be used to plan the main study. After a thorough evaluation of the pilot study's implementation by both the research team and the quality control team, the accuracy and reliability of the collected data were confirmed. Consequently, it was determined that the methodology employed in the pilot study will be adopted for the ongoing research.

Participants from the pilot phase will be included in the final analysis, ensuring continuity and robust data integrity. Consequently, we increased our sample size to 21,000 participants.

Eligibility criteria

Participants eligible for this trial complied with all the following at randomization: I. aged between 35 and 70 years; II. lived in the Ardabil province for the last 10 years; III. willing to participate in the study and undergo the procedures and treatments described in the protocol; IV. willing and able to provide informed consent; V. willing to provide biological specimens. Patients were excluded from the study if they met the criteria: I. pregnancy; II. history of peptic ulcer disease and gastrointestinal (GI) bleeding/perforation; III. severe dyspepsia; IV. prior gastric or esophageal malignancy or gastrectomy; V. known allergy to any of the study medications; VI. known medical conditions that preclude antibiotic therapy in the case of *H. pylori*-positive participants; VII known medical conditions that could limit life expectancy (HIV/AIDS, congestive heart failure, renal failure, hepatic failure, current or prior malignancy).

Interventions

The first dose of the study medication will be delivered to the participants after receiving the negative *H. pylori* test. The study has two arms of treatment (aspirin) and control (placebo), receiving either a once-daily 81 mg enteric-coated aspirin tablet or a placebo with the same instruction for 10 years. Participants will receive full written guidance on the administration of medications, possible side effects, and appropriate actions.

Outcomes

Outcomes will be measured 5 years after the end of treatment. The primary outcome of interest in AGCPT is the difference between the two interventional arms in the proportion of the cumulative incidence rate of GC. The incidence of GC is defined as the proportion of participants who develop new GC, diagnosed by hospital documents, cytopathological reports, or death certificates. Secondary outcomes of interest during the intervention timeframe until 5 years after the end of treatment consist of I. the incidence rate of precancerous gastric lesions (intestinal metaplasia and atrophic gastritis); II. adverse events (any medical events, hospitalizations, diagnostic and therapeutic care, and all-cause mortality) may occur; III. any side effects related to intervention drugs; and IV. any risk or protective factor associated with GC that is determined by a comprehensive assessment of various general, physiological, lifestyle, medical, nutritional, and environmental factors.

Participant timeline

After taking verbal consent and signing written informed consent, eligible participants will be initially tested regarding their *H. pylori* status using *H. pylori* stool antigen test. Participants with positive tests will be treated by one of the standard treatment regimens at the physician's discretion based on bacterial resistance, allergic reactions (pruritus, urticaria), and other concomitant medications used for 2 weeks. These four-drug regimens are displayed in Table 1. Participants will return to the study site 8 weeks later and repeat their test for confirmation of a successful *H. pylori* eradication. Otherwise, another regimen will be prescribed until the subjects will become infection-free. Another test will be performed 8 weeks after eradication, and all *H. pylori*-negative participants will be allocated into either of the study arms. The recruitment will last about 2 years; all participants will receive aspirin or placebo for 10 years. Follow-ups will be every year regarding side effects and the supply of study drugs. The primary outcome will be investigated 5 years after the end of the intervention. The workflow of the AGCPT study is shown in Fig. 1 and each step will be done in the same order as shown in the chart.

Sample size

Based on the formula below, considering the assumptions of the power of 0.8 and 30% non-response or loss to follow-up, 35% decreased mortality due to aspirin, $\overline{p} = 0.03$ (gastric cancer mortality after 10 years), for each arm (m) 10,500 participants were calculated, with the total sample size of 21,000 participants.

$$m = \frac{2(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{\log(OR)^2 \overline{p}(1-\overline{p})}$$

Table 1 Four standard regimens for *Helicobacter pylori* eradication

Regimens	Agents	Dose	Duration
Furazolidone	Omeprazole	20 mg BID	Daily for 14 days
	Amoxicillin	1000 mg BID	Daily for 14 days
	Furazolidone	200 mg BID	Daily for 10 days
	Bismuth subsalicylate	240 mg BID	Daily for 14 days
Clarithromycin	Omeprazole	20 mg BID	Daily for 14 days
	Clarithromycin	500 mg BID	Daily for 14 days
	Amoxicillin	1000 mg BID	Daily for 14 days
	Bismuth subsalicylate	240 mg BID	Daily for 14 days
Rofaxan	Omeprazole	20 mg BID	Daily for 14 days
	Rofaxan	550 mg BID	Daily for 14 days
	Amoxicillin	1000 mg BID	Daily for 14 days
	Bismuth subsalicylate	240 mg BID	Daily for 14 days

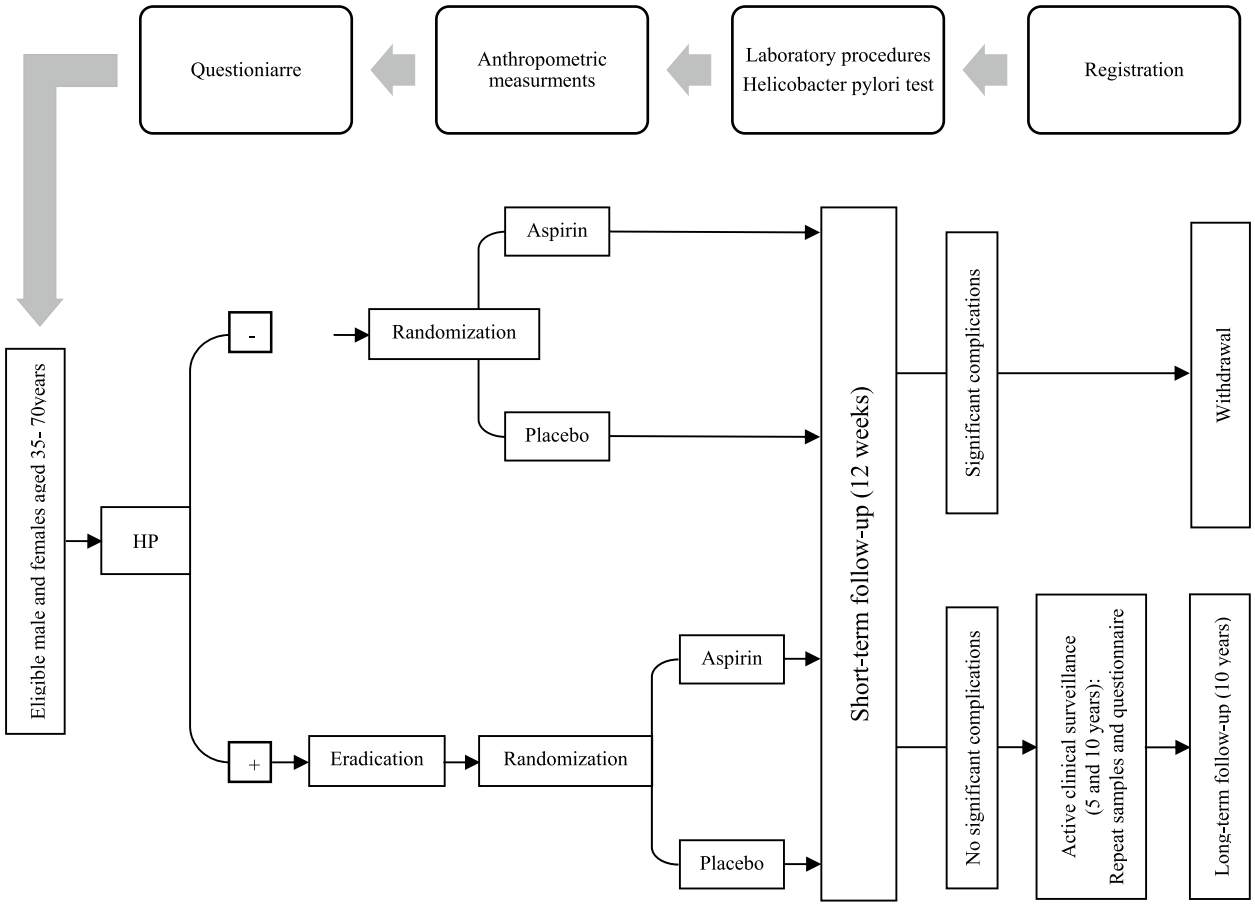

Fig. 1 Flow of participant enrollment, HP eradication, randomization, and follow-up

Recruitment

Trained personnel contact or visit local primary care centers, called "Health Centers" and provide them with a general explanation of the study and participant characters. Based on the health records, Health Center's physicians will be asked to randomly refer individuals who meet the eligibility criteria to the DDRC for recruitment. If individuals initially agree to participate, they will be contacted later to set an appointment date and informed about the study process. The initial plan for the recruitment and enrollment phase aimed to enroll up to 21,000 participants. However, the onset of the COVID-19 pandemic significantly disrupted these timelines, resulting in delays that extended the completion of this crucial phase. As a consequence of the evolving public health landscape, researchers faced unforeseen challenges that impacted participant recruitment and data collection efforts, necessitating adjustments to the project's overall schedule. This situation underscores the broader implications of the pandemic on ongoing research endeavors, highlighting the need for adaptive strategies in the face of such global crises.

Assignment of interventions

Allocation

Eligible participants will be randomly assigned to aspirin or placebo groups with a 1:1 allocation ratio using permuted block randomization. Randomization was done based on *Helicobacter pylori* status. People who are *Helicobacter pylori* negative (people who were negative at the beginning of the study or became negative after eradication) were randomly divided into two groups. After registering a negative answer for *H. pylori* infection, the application designed for the online interview generates a code for the person, which is printed and given to the participant. This code (unchangeable by the researcher and interviewer group) is given to the pharmacy by the participant and the drug is delivered to them based on the code.

Blinding

The provided medications, including aspirin and placebo, are small-sized white tablets. Aspirin and placebo bottles are entirely the same and labeled "Artamed." Both bottles contain 120 tablets, and the manufacturer prints a code on each bottle which can be used to determine the type of medication inside them. The codes were concealed in sealed and opaque envelopes with printed corresponding randomization numbers and kept safely in the study site with the personal investigator. DDRI provides and relabels the study drug and placebo to maintain the masking of the contents. The trial participants and care providers are blinded to the allocation. Staff independent of the study conduction enter data in the database using participants' randomization codes so that outcome assessors and data analysts remain unaware of the treatment groups. The data and safety monitoring board will have full access to the data at any time upon sending a formal request to the personal investigator.

Data collection, management, and analysis

Data collection

Upon the arrival of the invited individuals at the study site, reading information pamphlets, and obtaining written informed consent, participants will be registered using credible personal identification documents. A unique barcode will be issued for labeling all biological samples and documentation. Laboratory specimens: As participants are fasting, the next step after registration will be the collection of biological specimens from each individual. Twenty-five milliliters of the blood sample will be collected using vacutainers, centrifuged (3000 rpm, 15 min), and fractioned into different aliquots. All aliquots will be tagged with participants' unique barcodes and stored in ultra-freezers (− 80 °C). A small amount of blood will be used for blood and biochemistry tests, including complete blood count (CBC), fasting blood sugar (FBS), total cholesterol (Chol), low-density lipoprotein (LDL), high-density lipoprotein cholesterol (HDL), triglycerides (TG), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), blood urea nitrogen (BUN), and creatinine (Cr). Stool samples will also be collected to *H. pylori* antigen (in vitro diagnostic test, Toyo®, Turklab, Turkey). Urinalysis will be performed regarding pH, specific gravity, and the presence of blood, protein, glucose, bilirubin, nitrates, ketones, ascorbic acid, leukocytes, and microalbumin. Hair and nail samples also will be stored in the Biobank (Table 2). Anthropometric data will be acquired as the next step after sample collection because of the minimum measurement error/bias rate in the morning. Height (cm), weight (kg), and waist, hip, and wrist circumferences (cm) will be measured using US National Institutes of Health protocols. Afterward, participants will be interviewed using a standardized and validated questionnaire of general data, medical conditions, nutritional information, and GI-specific variables completed online. The validity and reliability of the questionnaire were assessed in a previous study [21]. The general questionnaire includes demographic characteristics, socioeconomic status, occupational status, fuel exposures, lifestyle, sleep and circadian rhythm, and physical activity. The questionnaire assesses past medical history, reproductive history in females, medication history, family history, oral and dental health, personal habits (smoking, alcohol, and drug use), history of chronic diseases, and a thorough physical examination. The nutritional questionnaire includes a validated food frequency questionnaire about the consumption of bread, cereal, meat products, dairy products, vegetables, and fruits, oils, and sugars in the past year. Additionally, supplement and water intake, dietary habits, and food preparation and storage techniques during the past year were questioned.

After administering medications, patients will be followed weekly for 12 weeks to determine complications in the initial short-term follow-up. In case of no significant complications, the long-term follow-up will start after this 12-week period and will continue for 10

Table 2 Types of biological samples collected from each individual

Sample type	Amount	Storage condition
Blood	25 ml	- All blood samples are stored in − 80 °C freezers - Whole blood: two 1.5-ml cryotubes and one 1-ml cryotube (Micronic, Lelystad, the Netherlands) - Plasma: two 1.5-ml cryotubes and five 1-ml cryotubes - Buffy coat: three 0.5- to 1-ml cryotubes
Stool	5 ml	
Urine	5 ml	1.5 ml stored in − 80 °C freezers
Hair	200–300 strands, 1–3 cm long	Stored in foil and zip-lock bags in a cool, dry location
Nail	All fingernails and toenails	Stored in foil and zip-lock bags in a cool, dry location

years. During these 10 years, participants will be regularly contacted every year to determine adherence, outcomes, complications, and adverse events. Also, at 5 and 10 years endpoints, 10% of the participants will undergo again repeating sampling, primary measurements, and a short follow-up questionnaire (Fig. 1). Patients may discontinue the study, and consequently the intervention, at any time upon the investigators' opinion concerning the participant's safety and well-being, the wish of the participant, or when the participant is lost to follow-up. Adherence will be assessed by a self-report questionnaire, pill count (every 4 months), and measuring aspirin ingredients in blood and urine samples in a subsample (1000 participants).

Data management

Paper study forms were designed and filled out during patient recruitment. Core center-designated employees enter all data electronically into a local clinical data management system. Participants' original records have been stored securely and in an accessible place and manner in an office at the study site. Any modification to data registered in the dataset will be questioned and documented. Our designed system detects smartly missing data or specific errors and reminds follow-up points. The data manager checks then the original forms for errors, inconsistency, and missing data and discloses it. The quality assurance and quality control team approved the data entry, and data integrity was assured after repeated data checks and cleaning.

Statistical methods

The intention-to-treat analyses will be used for the primary and secondary efficacy analyses. Endpoints will be determined for all patients who underwent the final after 10 years of samplings, measurements, and a short follow-up questionnaire. The primary analyses will utilize an intention-to-treat analysis based on the difference in the incidence proportion of GC between the intervention group (aspirin) and the control group (placebo). Secondary analyses will include case–control comparisons that aim to investigate the role of risk factors in the occurrence of GC. Frequency, percentage, and 95% confidence intervals (CIs) were used as descriptive statistics for categorical variables to summarize the characteristics of the study population. The chi-squared test will to compare categorical variables, and the *T*-test for continuous variables. Explanatory variables found to have a significant association with the incidence of GC in the univariate analysis will be further adjusted through multivariable logistic regression models. The odds ratios (ORs) and their 95% CI will be calculated by logistic regression analysis to measure the strength of the association. Model-based standardization, marginal causal interpretation, and time-trend analyses will be other analyses used to interpret our results. Multiple imputation methods will be used to deal with missing data. A p value below 0.05 will be considered statistically significant. Randomization, data curation, and all statistical analyses will be conducted using R programming language version 4.1.1 or the updated version at the time of analysis (R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/).

Monitoring

Data monitoring

The quality control and assurance measures were implemented centrally by an independent Data Safety and Monitoring Board (DSMB) consisting of clinicians and a biostatistician to ensure that all procedures would be under the protocol. The DSMB has complete, up-to-date access to all participant data upon request and will be reported regularly about any response information, any unexpected adverse events, and audit results. Any other information will be provided upon request, as well. An independent statistician blind to the treatment assignment will supply an interim analysis on the primary endpoint to the DSMB when 5 years of follow-up are completed. The interim analysis will include the presentation of the number and percentage of individuals recruited, summaries of baseline characteristics of recruited participants, and compliance with study medication, separately by the randomized group. Accordingly, the DSMB and the study organizers will then jointly decide on the termination/continuation or amendment of the trial in case of noticeable statistical differences in the efficacy of aspirin between arms or safety issues. To deal with loss to follow-ups, the surveillance unit monitors the attendance of participants to receive drugs through the information registration system and calls the participants if they do not attend. Suppose a participant wishes to refrain from participating in the study. In that case, the reason for unwillingness will be recorded, and the statistics will be reported to the principal investigator in weekly reports and online access.

Harms

During the follow-up period, participants will be regularly contacted every year to determine outcomes and complications. All adverse events and side effects will be recorded immediately after subject enrollment and on a self-report basis. An adverse event is defined as any unfavorable medical occurrence in a subject with or without the possibility of a causal relationship with intervention, including any side effects related to study drugs, the incidence of any medical events, hospitalizations, diagnostic

and therapeutic care, and occurrence of death. In case of serious events or diagnosis of a major disease, investigators will follow the phone call with a house/hospital visit to perform a more thorough follow-up. A copy of all pertinent medical documents for further evaluation and documentation will be obtained. A team of three internists will evaluate documents and patients to confirm a diagnosis. The investigators must report serious adverse events to the responsible, ethical committee.

Auditing

The central quality assurance and quality control team, consisting of study monitors and coordinators, is responsible for auditing the overall accuracy and completeness of the data collection process and is consistent with the requirements of the protocol. The essential factor in this regard is an intelligent data server, which limits many common errors that will be made during the data entry process. At the beginning of the trial, the monitors conducted a tutorial on the data entry system. They educated coordinators in all aspects of data entry for full daily supervision of the enrollment and remote checking of the dataset to spot missing information and errors on this server. The monitors made routine surprise on-site inspections to evaluate workflow and staff performance, review the source documents and validate the data quality, verify the correct documentation of adverse events, examine interviewees and coordinators, and solve untoward problems.

Furthermore, random participants completed opinion surveys, and some fixed variables were reassessed for double-checking. In addition, the monitors listened to occasional secret voice/desktop recordings of the interviewer's performance with the interviewee's consent. Reports of these evaluations were sent to the principal investigator and the DSMB.

Ethics and dissemination

Research ethics approval

Ardabil University of Medical Sciences reviewed and approved the study protocol, the informed consent forms, and all recruitment materials (Ethics committee reference number: IR.ARUMS.REC.1395.135), concerning scientific content and compliance with regulations of research and human subjects. This protocol has also been registered in the Iranian Registry of Clinical Trials (IRCT201105082032N3). Progress, efficacy, and safety data will be regularly reported to the same committee. The responsible ethics committee will be formally notified of any modifications to the protocol before implementing such change.

Protocol amendments

In educational meetings, the study personnel will be asked to report if they encounter any problems in running the study protocol. If they were any violations, the principal investigator would ensure to make procedures to prevent them. A full report of the violation and the addressed preventive measures will be sent to the monitoring unit, institutional review board, and ethics committee within 1 week. During the study, if the study investigators conclude that changes should be made to the study protocol, it must first be approved by the steering committee. After that, the updated protocol will be sent to the monitoring unit, institutional review board, and Iranian Registry of Clinical Trials (IRCT). After obtaining the permissions, the executive units of the study will be notified of the protocol amendments.

Consent

Trained research interviewers will explain the main aspects of the trial to participants in-person regarding the objectives, rationale, interventions, outcomes of interest, data collection process, and safety by using publicly understandable terms and language. Participants will receive detailed information sheets and will be able to discuss their ambiguities and concerns with the interviewer. Written informed consent will be obtained from those willing to participate in the trial. Informed consent form is not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the authors on request.

Confidentiality

All study participants' data have been deidentified using a unique code number instead of names or other identifying information. All biological specimens and paper forms were labeled and linked by participants' ID numbers and stored securely at the study site with limited access. Data are stored in a centralized database with password-protected access systems, and the data management group supervises the data-sharing process. The principal investigator has direct access to the final cleaned dataset. Moreover, the quality control and quality assurance team and data analysts can access the full trial dataset. Deidentified data access might be possible for other investigators and team members with a formal request describing their plans.

Access to data

The trial results will be available to the public, participants, and healthcare professionals via publication in an appropriate journal at the planned target of 5 years after the end of treatment, if the circumstances warrant.

Discussion

Despite all treatment advances and the declining trend in the incidence and mortality rates of GC over the past decades [22], GC remains an ongoing global health challenge with an unfavorable prognosis. Since the current therapeutic measures are often ineffective and unsuccessful at advanced stages, when the majority of cases of GC are diagnosed, the best results appear to be obtained from pursuing an efficient preventive strategy consisting of regular screening and surveillance programs for the detection of early pathologic alterations, modification of known risk factors, and chemoprophylaxis. One of the potential protective agents against GC is aspirin. Thus, we designed this study to identify the effect of long-term low-dose aspirin use on the prevention of GC following *H. pylori* eradication.

Aspirin is one of the most widely used medications in the world [23]. Regular long-term aspirin use reduces the risk of numerous age-associated conditions in people over 50. First and foremost, the efficacy and safety of aspirin were established in preventing myocardial infarction, ischemic strokes, and vascular death in those at higher risk of cardiovascular events [24, 25]. Furtherly, aspirin was observed to have an inverse correlation with the incidence and mortality rates of certain types of cancers, possibly through the blockade of the cyclooxygenase (COX) pathway [15, 26, 27]. A potential mechanism for the anti-neoplastic activity of aspirin is through the inhibition of cyclooxygenase-2 (COX-2) production [27]. COX-2 isozyme, which was revealed to be overexpressed in several GI malignancies [28–30], mediates some key cellular carcinogenic activities, such as inhibition of the apoptosis in GI epithelium, the proliferation of cancer cell lines, and angiogenesis [31–34]. Other than the COX pathway, aspirin downregulates the survivin protein (a negative regulator of apoptosis), which leads to increased apoptosis of the human GC cell line (SGC-7901) [35]. That is why nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, may be potential agents for the chemoprevention of GC.

Overall, the greatest anticancer properties of aspirin have been noticed in the risk reduction of GI neoplasms, especially in colorectal cancers [15, 36, 37] such that the United States Preventive Services Task Force has recommended a low-dose aspirin use for the primary protection against colorectal cancer alongside cardiovascular disease in high-risk populations aged between 50 and 60 years [38]. Aspirin might also reduce the risk of esophageal, gastric, biliary, endometrial, breast, and prostate cancer [15, 39–42]. Numerous observational studies have evaluated the association between aspirin intake and GC risk and highlighted its importance in cancer control. The estimated odds ratios of GC ranged from 0.3 to 0.7 in different case–control studies [18, 43–47] which means that a significant reduction in GC risk is possible with long-term use of aspirin, especially after 2, 5, or 10 years of aspirin therapy.

Ardabil, a northwestern province of Iran, has the country's highest incidence rate of GC, with an age-standardized incidence rate of 48.38 and 20.62 per 100,000 in males and females, respectively [4]. Additionally, based on a population-based study in the early 2000s, more than 89% of adults aged 40 or older were infected by *H. pylori*, a carcinogenic risk for GC [20, 48]. Regarding the high incidence and mortality rates of GC in Ardabil province and the potential cancer-preventing properties of aspirin, Ardabil population-based randomized controlled trial was designed to evaluate the effect of aspirin on GC prevention. Relying on the statistical nature of population-based studies, we hope that the AGCPT results can be generalized to the entire population to provide adequate evidence for healthcare policies. Among the strengths of the AGCPT study, we can mention I. our study location is a province with high incidence and mortality rates of GC; II. the willingness of most invited subjects to participate in the pilot study; and III. the prolonged aspirin use and follow-up timeframe. Since GC development is a long-term multistep and multifactorial process, it should be noted that the duration and continuity of aspirin use are determinative and critical variables in the assessment of the effect of aspirin on GC. Therefore, if any problem hinders the correct medication administration or recording of participant reports, loss-to-follow-ups may affect the quality of data. A surveillance unit will monitor the attendance of participants. Another limitation of the study is that as it is a clinical outcome-based population study, it is not feasible to provide information about the possible chemopreventive mechanisms of aspirin on GC. Therefore, conducting complementary studies to explain the possible mechanisms with a molecular precision medicine approach is recommended. The study's results help policymakers and researchers update the strategies for GC prevention and the plans for the broader use of aspirin as a chemopreventive medication.

Trial status

The latest protocol (version 3) was approved by the IRCT review board on January 3, 2023. The included participants have undergone the initial assessments and

procedures necessary for the study, and their data will be included in the final analysis to assess the study's outcomes. The recruitment of participants is ongoing, and further individuals who meet the inclusion criteria will be invited to participate in the study. The researchers will continue to track and monitor the progress of these participants throughout the study duration to ensure that any changes and outcomes are documented accurately. The approximate date when recruitment will be completed is April 2025.

Abbreviations

AGCPT	Ardabil gastric cancer randomized placebo-controlled prevention trial
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BUN	Blood urea nitrogen
CBC	Complete blood count
Chol	Total cholesterol
CI	Confidence interval
COX	Cyclooxygenase
COX-2	Cyclooxygenase-2
Cr	Creatinine
DDRC	Digestive Disease Research Center
DDRI	Digestive Disease Research Institute
DSMB	Data Safety and Monitoring Board
FBS	Fasting blood sugar
GC	Gastric cancer
GGT	γ-Glutamyl transpeptidase
GI	Gastrointestinal
H. pylori	*Helicobacter pylori*
HDL	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
IRCT	Iranian Registry of Clinical Trials
LDL	Low-density lipoprotein
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
TG	Triglycerides

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08455-5.

Additional file 1: SPIRIT checklist for the protocol of AGCPT.

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Authors' contributions
Study concept and design: FP, RM, AE, and AS. Acquisition of data: FP, HP, EF, and SP. Analysis and interpretation of data: FP, AE, and AS. Drafting of the manuscript: FP, AS, MMR, NR, RM, HP, and EF. Critical revision of the manuscript for important intellectual content: FP, MMR, AS, AY, AN, HP, EF, SH, NR, RM, HP, and BZ. Statistical analysis: FP, MMR, AE, and AS. Administrative, technical, and material support: FP, AS, AY, and EF. Study supervision: FP, AS, AY, RM, and EF. The authors read and approved the final manuscript.

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Availability of data and materials
Sharing of data is not relevant to this protocol article since no data has been produced or analyzed, yet. However, the manuscript includes information about plans to share data in the "Ethics and dissemination" section, specifically under the "Access to data" subheading. Informed consent form is not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the authors on request.

Declarations

Ethical approval and consent to participate
The study protocol, informed consent forms, and recruitment materials were reviewed and endorsed by the Ardabil University of Medical Sciences Ethics Committee (reference number: IR.ARUMS.REC.1395.135, the updated version: IR.ARUMS.REC.1403.179) for their scientific content and compliance with research and human subject regulations. Prior to any study-related procedures, a study physician will obtain written and signed informed consent from each participant.

Consent for publication
Not applicable.

Competing interests
There is no competing interests.

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