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DOI:
10.1093/eurheartj/ehab919

Title page

Polypill for Prevention of Cardiovascular Diseases with Focus on Non-alcoholic Steatohepatitis: the PolyIran-Liver Trial

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Abstract:

Background: Individuals with nonalcoholic steatohepatitis or elevated liver enzymes have increased cardiovascular mortality but are often excluded from prevention trials. We investigated the effectiveness of fixed-dose combination therapy for the prevention of major cardiovascular events (MCVE) among individuals with and without presumed non-alcoholic steatohepatitis (pNASH).

Methods: 2400 Participants over 50 were randomized into intervention and control groups. Consent was obtained post-randomization. Consenting participants in the intervention group were given a pill containing aspirin, atorvastatin, hydrochlorothiazide, and valsartan (polypill). Participants were followed for 5 years. pNASH was diagnosed by ultrasonography and elevated liver enzymes. The primary outcome was MCVE. ClinicalTrials.gov: NCT01245608.

Results: Among the originally randomized population, 138/1249 in the intervention group (11.0%) and 137/1017 controls (13.5%) had MCVE during the 5-year follow-up (unadjusted risk ratio [RR] 0.83, 95% confidence interval [CI] 0.66-1.03). Of the 1508 participants who consented to additional measurements and treatment, 63/787 (8.0%) intervention group participants and 86/721 (11.9%) controls had MCVE (adjusted RR 0.61, 95% CI 0.44-0.83). Although the adjusted relative risk of MCVE in participants with pNASH (0.35, 95% CI 0.17-0.74) was under half that for participants without pNASH (0.73, 95% CI 0.49-1.00), the difference did not reach statistical significance. There was no change in liver enzymes in participants taking polypill but among those with pNASH, there was a significant decrease after 60 months of follow-up (intragroup -12.0 IU/L, 95% CI -14.2 to -9.6).

Conclusion: Among patients consenting to receive fixed-dose combination therapy, polypill is safe and effective for prevention of MCVE, even among participants with fatty liver and increased liver enzymes.

Keywords: Cardiovascular diseases, primary prevention, secondary prevention, polypill

Introduction:

Non-alcoholic fatty liver disease (NAFLD) often simply referred to as "fatty liver", is a common condition affecting up to one-third of the population in South America, the Middle East, the USA, and Europe, and is an independent risk factor for cardiovascular disease (CVD).[1,2] CVD and fatty liver also share several behavioral and metabolic risk factors including central obesity, type 2 diabetes mellitus, metabolic syndrome, tobacco use, unhealthy diet, physical inactivity, and dyslipidemia.[3] Non-alcoholic steatohepatitis (NASH) is a subset of fatty liver disease in which hepatic inflammation is also present and is often accompanied by increased liver enzyme levels. Individuals with fatty liver, and especially those with NASH and elevated liver enzymes, have a considerably higher risk of CVD.[4,5] Therefore, such individuals may enjoy a greater benefit from primary prevention. Unfortunately, many key studies on primary or secondary prevention exclude participants with increased liver enzyme levels and, therefore, there is a paucity of data in this area.[6]

Despite concerns about the prescription of statins to subjects with NAFLD or elevated liver enzymes and normal lipid levels, current literature suggests that statins may even have beneficial effects on the liver itself.[7,8] There is also evidence that aspirin, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARB) might be beneficial for fatty liver.[9,10]

We have previously reported the effectiveness of the intervention on preventing major cardiovascular events (MCVE) of a four-component pill (polypill) that included 81 mg aspirin, 20 mg atorvastatin, 12.5 mg hydrochlorothiazide, and either 5 mg enalapril (PolyPill-E) or 40 mg valsartan (PolyPill-V) in a pragmatic cluster-randomized study in a rural population in Iran (PolyIran).[11] Unfortunately, this study lacked information on the liver status of participants. The current study is an extension of PolyIran in which we investigate the effects of the same polypill on the risk of MCVE in an urban community (Gonbad city). Instead of excluding them, we separately analyzed the effects on participants with increased liver enzyme levels and participants with fatty liver.

Methods:

Design and population

The PolyIran-Liver study is an open-label, individually randomized controlled trial nested within the Golestan cohort study (GCS).[12] The GCS is a population-based prospective cohort study run in the Golestan province of Northern Iran. It was launched in 2004 and included 50,045 participants aged 40-75 years at enrolment. GCS participants are followed up annually and all major cardiovascular and health events are recorded.

GCS participants older than 50 years and resident in Gonbad city were eligible for the PolyIran-Liver study. A random sample of participants over 50 years of age was selected from the GCS database and further randomized into two groups. After randomization, participants were invited for additional measurements and to assess their eligibility for polypill and to obtain consent. Seeking consent after randomization was first described by Marvin Zelen in 1979 and is commonly referred to as the Zelen design. In this design participants are first randomly allocated and then enrolled, allowing separate consent forms for intervention and control groups. A possible shortcoming of this design is that participants' consent may be influenced by their allocation to the intervention or control group, meaning there may be differences between the groups. Despite its shortcomings, this design is easier to implement and generally improves compliance of enrolled participants.[13]

In addition to analyzing results among the originally randomized population, we also compared the rate of MCVE among consenting participants who were eligible for polypill. We refer to this group as the consenting population (versus the randomized population). The randomized population includes participants not consenting to the additional measurements, those not meeting the eligibility criteria, and the consenting population. It represents the real-world population that would be offered intervention, many of which will decline or not be eligible. Studying this population will allow us to see whether polypill will help reduce MCVE in a real-world setting where many participants might not consent or not be eligible. It should be noted that all participants of the GCS have previously consented to gathering health and survival data and annual follow-up through the GCS.

Participants were followed for MCVE and overall mortality for 5 years. Details of the design, inclusion, and exclusion criteria have been published previously.[14]

Randomization and blinding

The urban population enrolled in the GCS and aged 50 years or older on October 2011 constituted the sampling frame. Of the 7,351 participants within the sampling frame, 2,400 participants were randomly selected using a computer-generated list with a sex ratio of 50:50.

The 2400 selected participants were further randomized to receive polypill once a day (intervention group) or no polypill (control group) at a ratio of 55:45. According to our previous experience with this population, we expected approximately 10% of the intervention group not to consent to the intervention. Thus, the randomization ratio of 55:45 was chosen to achieve a 50:50 ratio after consent.

In this pragmatic trial, allocation was not concealed and participants and the enrolment team were not blind to the allocation. However, the team assessing the primary and secondary outcomes was blind.

Procedures

Following randomization, participants in intervention and control groups were contacted by telephone and invited for participation in the study. For those accepting the invitation and attended the eligibility assessment visit, written consent was obtained and laboratory tests, ultrasonography, and liver stiffness measurements (LSM, FibroScan, Echosense, France) were performed. Ultrasonography and liver stiffness measurements were each performed by a single operator for all participants. Participants were identified as having presumed NAFLD (pNAFLD, fatty liver) if suggested by ultrasound. If in addition to fatty liver, participants had elevated alanine aminotransferase (ALT) levels (over 30 IU/L in men and 20 IU/L in women) they were identified as presumed NASH (pNASH). Participants with alcohol use and active hepatitis B or C were excluded. Other exclusion criteria included contraindications to the constituents of the polypill.

Participants in the intervention group who agreed to participate and met eligibility criteria received a once-daily supply of PolyPill V (Alborz Darou Pharmaceutical Company; Tehran, Iran) which includes 81 mg aspirin, 12.5 mg hydrochlorothiazide, 20 mg atorvastatin, and 40 mg valsartan. They were advised to take the pill at bedtime but were free to take it at any other time if they or their physician chose. A one-day supply was provided and they were instructed to return on the following day for evaluation of immediate adverse events (run-in period). One

other reason for implementing the run-in period was that based on our previous experience we knew that some participants would consent to the study only because they felt obliged to cooperate with the researchers in return for the free tests they were receiving and did not truly intend to go through with the study. Participants who complied with the run-in period without any immediate adverse events were enrolled in the study and provided with a supply of polypill. Thus, only participants randomized to the intervention group who consented to the study, met eligibility criteria, and completed the run-in period received the polypill. Participants in both groups continued taking medications prescribed before entering the trial. Details of handling participants already on components of the polypill has been previously published.[14]

Participants in both groups were visited every 6 months for 5 years. In each follow-up visit, anthropometric and blood pressure measurements were performed. The participants were also asked to fill out a short questionnaire about possible adverse events and additional medicine use. Participants who were found to have high blood pressure (systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg) in a follow-up visit were referred to their physician for further evaluations. In the case of the intervention arm, there were two additional visits at months one and two to check for important adverse events. Furthermore, a pill count was performed in each follow-up visit to measure compliance. At the end of the 5-year follow-up period, laboratory tests, ultrasonography, and liver stiffness measurements were repeated.

The randomized population was followed annually by the routine GCS follow-up team for primary outcome and overall mortality.

Endpoints

The primary endpoint was the occurrence of an MCVE which was defined as fatal myocardial infarction, sudden death, new-onset heart failure, coronary artery revascularization procedures, fatal and non-fatal stroke, or hospitalization for an acute coronary event.

Secondary endpoints included all-cause mortality, individual components of the primary outcome, and changes in blood pressure, low-density lipoprotein (LDL) cholesterol, liver stiffness, liver enzyme levels, compliance, and adverse events.

Investigators assessing primary and secondary endpoints were blinded to the allocation group of participants. Details of endpoint assessment have been previously published.[11,14]

Statistical methods

The justification of sample size has been previously described.[14] We determined that the contributed samples provided 80% power to detect a risk difference of an MCVE of 3.5%. The samples contributed provided more than 95% power to detect a 2 IU/L difference in ALT after 30 and 60 months between the intervention and control groups, assuming a standard deviation of changes from baseline of 10 IU/L.

Baseline characteristics were compared between study arms using the chi-square test for categorical variables and independent t-test or non-parametric Mann-Whitney U test for quantitative variables. Diabetes was defined as a fasting blood sugar ≥126 mg/dL, use of anti-diabetes drugs, or self-report of a physician diagnosis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, self-report of a physician diagnosis, or use of antihypertensive drugs in participants without a history of CVD.

The analysis was done in two parts. The first part was the intention-to-treat analysis of the primary outcomes and overall mortality for the randomized population. This analysis included all randomized participants including those who did not show up for additional measurements or those not eligible or not consenting to treatment. All these participants had previously, on enrollment to the GCS study, consented to collection of data on the primary outcomes and overall mortality. The second part of the analysis was on primary and secondary outcomes in the consenting population, including changes in liver-related variables (ALT, aspartate aminotransferase [AST], and liver stiffness measure [LSM]) and other measurements conducted for these participants.

We compared the risks of all MCVE, non-fatal CVD, CVD-related mortality, and overall mortality between the intervention and control groups. We used the Poisson regression model with a robust variance to obtain both adjusted and unadjusted relative risk (RR) and 95% confidence intervals (Cis). Adjusted and unadjusted risk differences (RD) and 95% CIs were obtained using binomial regression with identity link function. Adjustments were made for

variables that differed between study groups including smoking status (ever used vs. never used), history of CVD, and baseline cholesterol.

To evaluate the effect of the polypill on cardiovascular outcomes in participants with liver problems, we performed pre-specified stratified analyses by three liver-related variables: fatty liver (pNAFLD); pNASH; elevated ALT levels only; and additionally, on LSM ≥7 KPa which indicates significant fibrosis. Furthermore, subgroup analyses were performed by sex, body mass index (BMI) category (normal, overweight and obese defined as <25, 25 to 29.9, and ≥30 kg/m^2, respectively), age groups (≤65 years and >65 years), pre-existing CVD, pre-existing hypertension, pre-existing diabetes mellitus, history of smoking (ever used vs. never used) and baseline cholesterol (≤198 mg/dL and >198 mg/dL). The risk of MCVE was also compared between the intervention and control groups stratified by duration of follow-up interval (months 0–30, and months 31–60).

We also analyzed the adherence to polypill as measured by pill count. Adherence to polypill was calculated by dividing the number of pills used by the participant by the number of pills supplied and was categorized into high (≥70%) and medium or low (<70%). To assess the association of adherence to polypill tablets with baseline covariates we obtained the odds ratios and 95% CIs with multiple logistic regression model.

For secondary outcomes, changes in liver function parameters, blood pressure, lipid profiles, and BMI were analyzed using a generalized linear model and log transformations for variables with non-normal distribution. We also evaluated the changes in liver function parameters in participants with pNASH. We analyzed changes from baseline in three models: the first was only adjusted for baseline values of that outcome; the second was further adjusted for age, sex, pre-existing CVD, and diabetes mellitus; and the final model was further adjusted for baseline CVD medication (including lipid-lowering drugs, anti-hypertensive drugs, and aspirin).

An interim analysis 30 months after enrolment found no serious adverse effects and the monitoring committee agreed to complete the 5-year follow-up. All analyses were done with Stata software (version 12) and p-values <0.05 were considered statistically significant.

The study complies with the Declaration of Helsinki and informed consent was obtained from all participants. The study protocol was approved by the institutional review board of the Digestive

Diseases Research Institute of Tehran University of Medical Sciences and ethics committees at Tehran University of Medical Science and the Ministry of Health and Medical Education (Tehran, Iran). The study is registered at ClinicalTrials.gov, ID: NCT01245608.

Results:

We randomly selected 2400 participants from the urban population of GCS who resided in Gonbad city. This population was randomly allocated to the intervention or control group with a ratio of 55:45 (1320 individuals in the intervention and 1080 in the control group). Of these, 134 individuals had migrated or died and were excluded: 71 (5.4%) in the intervention group and 63 (5.8%) in the controls, leaving 2,266 (94.4%) participants available for the study. The socio-economic, demographic, and measurement characteristics were similar between the two groups when they were originally enrolled into the GCS in 2004[14] (Table 1). We invited all 2,266 participants for eligibility assessment between October and December 2011.

Of the 2266 randomized participants invited for the eligibility assessment 404 declined to participate (refused consent): 218 (17.5%) intervention and 186 (18.3%) controls. In addition, 156 (15.1%) in the intervention group and 110 (13.2%) in the control group did not meet eligibility criteria. This left 875 (84.9%) in the intervention group and 721 (86.8%) in the control group. Of those in the intervention group, 88 (10.1%) did not continue to take the polypill after the one-day run-in and finally, 787 were enrolled in the intervention group and received polypill (Figure 1). Details of the enrollment process have been published previously[14]. The baseline characteristics of enrolled and excluded participants are given in Table 2.

A total of 1,508 individuals were enrolled in the consenting group; 787 in the polypill arm and 721 in the control arm, with a mean age of 58.6 and 59.4 years, respectively. 396 (50.3%) of the participants in the intervention group and 376 (52.2%) in the control group were men (Table 2). All baseline characteristics were similar between the two arms except for smoking, pre-existing CVD, and baseline cholesterol. Individuals in the intervention group were less likely to smoke but more likely to have pre-existing CVD and higher cholesterol levels (Table 2).

Primary outcome, individual components of the primary outcome, and overall mortality were evaluated for the randomized population. 137 of 1017 in the control group (13.5%) and 138 of 1249 in the intervention group (11.0%) had MCVE during the 5-year follow-up (unadjusted RR 0.83, 95% CI 0.66-1.03 and RD -0.02, 95% CI -0.05 to 0.00) and the findings changed little and remained non-significant after adjustment for age, sex, and previous history of CVD (Table 3, graphical abstract). It should be noted that since all randomized participants did not consent to additional measurements, some secondary endpoints were only available for the consenting population. For the same reason, subgroup analysis for pNAFLD and pNASH was not possible in the randomized population.

In the consenting group, after adjusting for smoking, baseline cholesterol, and pre-existing CVD the preventive effect of polypill was statistically significant (adjusted RR 0.61, 95% CI 0.44-0.83). We also observed a significantly lower risk of fatal MCVE, non-fatal MCVE, and all-cause mortality in the intervention group as compared with controls. In stratified analysis with respect to age, sex, BMI, baseline cholesterol, smoking, and pre-existing CVD, hypertension, and diabetes, there were no statistically significant interactions between study arms and subgroups (supplementary Table S1). After dividing the follow-up time into two intervals (months 0–30, and months 31–60), the results were similar between the intervals (supplementary Table S2).

In subgroup analysis, the RR of MCVE was less than half in participants with pNASH (adjusted RR 0.35, 95% CI 0.17-0.74) versus those without pNASH (adjusted RR 0.73, 95% CI 0.49-1.00) although this difference did not reach statistical significance. Similarly, the observed larger preventive effect of polypill in participants with pNAFLD, elevated ALT, and LSM ≥7 KPa was not statistically significant (Table 4).

Among subjects who received polypill, adherence was calculated at each follow-up visit and for the entire duration of study. We observed that adherence decreased over time (supplementary Figure S1). The median adherence among participants in the intervention group was 80.4% (Q1-Q3: 31.2-93.1) and 437 (55.5 %) were in the high-adherence group (used more than 70% of provided pills). High adherence was related to male sex, pre-existing hypertension, and presence of fatty liver at baseline (Supplementary Table S3). The risk of MCVE was significantly lower in

participants with high adherence as compared with controls (adjusted RR 0.46, 95% CI 0.30-0.71, Supplementary Table S2) as well as when compared with the low adherence group (adjusted RR 0.53, 95% CI 0.33-0.86).

Secondary outcomes included changes in liver enzymes and liver stiffness. In the consenting group, for whom additional measurement were available, we did not observe any significant difference between changes in ALT, AST, and LSM from baseline to months 30 and 60 between the study arms (Table 5). When only considering participants with pNASH, there was a greater reduction in ALT level in the intervention group versus controls at both months 30 (mean change 3.3 IU/L [95% CI 0.1 to 6.6]) and 60 (mean change 1.9 IU/L [95% CI -1.3 to 4.9). Changes in AST and LSM were similar between the two study arms in months 30 and 60 (Table 5, Supplementary Figure S2).

In the consenting intervention group, as compared to controls, we observed a significant reduction in systolic but not diastolic blood pressure at month 30 and diastolic but not systolic blood pressure at month 60. All lipid profiles (total cholesterol, LDL, and triglyceride) had a greater reduction from baseline in the intervention group at both months 30 and 60 (Table 6).

The incidence of different adverse events was similar between the two arms throughout the study. The frequency of adverse events decreased over time except for dyspepsia and cataract which remained fairly constant after month 18 (Supplementary Figure S3).

In Table 7 we compared the results from this study and our previous PolyIran study.[11]

Discussion:

In this pragmatic individually randomized controlled trial, we observed a statistically insignificant 17% RR reduction in MCVE among the randomized population. However, among subjects who consented to additional measurements and received polypill, our results showed a statistically significant 39% reduction in the risk of MCVE with similar reductions in CVD-related and all-cause mortality. The reduction in the risk of MCVE was greater in the participants with high adherence to polypill. The effects on MCVE in this group were consistent with our previous PolyIran study (adjusted hazard ratio 0.66, 95% CI 0.55-0.80), which had the same

entry criteria and used the same fixed-dose combination but was conducted in a rural setting as a cluster-randomized controlled trial.[11] These results were also close to other polypill studies, in particular the aspirin containing arm of the TIPS3 study in which the reported hazard ratio for MCVE was 0.69 vs our observation of 0.60.[15]

After 5 years, we observed a significant decrease of 36% in LDL cholesterol levels of the intervention group which is as expected for the dose of atorvastatin used in our polypill (20 mg) and in line with the suggestion from the literature to decrease LDL by 30-49%.[16,17] But surprisingly, the decrease in blood pressure of the intervention group was not greater than controls (Table 6). A less than anticipated decrease in blood pressure was also observed in the PolyIran study.[11] It is expected that valsartan at the dose of 40 mg would decrease systolic blood pressure by 5.7 and diastolic blood pressure by 2.8 mmHg.[18] The minimal decrease in blood pressure observed in our and the PolyIran study might be due to the fact that most subjects had normal blood pressure at enrollment. Furthermore, it might be related to the high salt intake among Iranians which is almost twice the World Health Organization recommendation.[19] Other possible reasons include development of tolerance to pharmacologic agents and non-adherence happening over the 5-year follow-up period.

The analysis of the randomized population is less likely to be attributable to selection bias. In this group we found that those randomized to receive polypill had an 17% reduction of MCVE but the difference was not statistically significant. It should be noted that only 63.0% of the 1249 participants in the pre-consent intervention group actually received polypill as many did not consent to the study or had exclusion criteria. This greatly dilutes any true effect of polypill and explains the non-significance we observed in this group. It also indicates that if polypill is to be used effectively as a strategy to reduce MCVE in a real-world setting, steps should be taken to increase acceptance.

An important advantage of our study is that we included participants with increased liver enzyme levels. Such participants are often excluded from trials of statins and other prevention studies. In fact, in this group, we observed similar reductions in MCVE as well as a reduction in ALT indicating that it is both safe and effective to use these drugs in individuals with liver enzyme elevations.

Another important finding of our study was the effect of polypill on the liver of participants with fatty liver. We observed that within the intervention group, although no overall changes in ALT were observed in consenting participants or in those with fatty liver, those with pNASH had a statistically significant decrease of ALT levels of 10.5 and 12 IU after 30 and 60 months of polypill, respectively (Table 5). The pNASH participants in the control group also had a decrease of ALT but the change was significantly less. This improvement in ALT of pNASH participants with polypill not only further confirms the safety of statins in this subgroup but also demonstrates a beneficial effect on the liver similar to that reported in the literature.[7,8,20,21] We did observe some reduction in AST and liver stiffness although it did not achieve statistical significance (Supplementary Figure S2). This can be explained by the fact that both AST and liver stiffness are indicators of fibrosis which takes a long time to resolve. A longer study would be required to identify changes in AST or LSM.

One of the major benefits of combination therapy is better compliance. It is much easier to take one pill rather than four as confirmed by early polypill studies that used adherence as a primary outcome.[22] Adherence to polypill in our study was relatively high. The median of adherence in the intervention group throughout the study was 80% which is slightly higher than those reported by Thom et al[22] and Selak et al[23] over the same follow-up interval. This could be due to the trust built up among participants by conducting this trial in the GCS setting with more than 15 years of follow-up.

We observed that adherence was associated with male sex, pre-existing hypertension, and fatty liver. We believe better compliance in hypertensive and fatty liver participants was because these individuals, knowing that they had some health problem, were more motivated. We have no explanation as to why male participants were more compliant which is opposite to previous reports.[24]

Limitations

One of the limitations of our study is the lack of placebo control and allocation concealment. Participants and the enrolment team who assessed the eligibility criteria were not blind to the participant's allocation. Lack of allocation concealment might result in the enrollment team, fearing adverse events, being inclined to exclude more participants on the intervention group

than controls. However, the exclusion criteria were defined objectively and there were no significant differences in the baseline characteristics of participants excluded from either of the study arms suggesting that lack of allocation concealment has not significantly affected our results.

One other limitation is less participation in the control group as compared to intervention in the final follow-up visit (56% vs. 76%) when laboratory and imaging studies were repeated. It appears that participants not receiving intervention were less inclined to continue with follow-up. As the primary outcome of our study was assessed separately by the GCS follow-up team which had a similar participation rate between groups, the lack of follow-up would have only affected our secondary outcomes.

Another limitation of our study is the definition of fatty liver and NASH. These are histologic terms and can only be used with certainty if liver biopsies are performed. Obviously, this is not an option for a study being performed on healthy individuals. Our best option was to "presume" NAFLD or fatty liver when ultrasonographic evidence suggested so knowing that up to 30% of fatty liver cases might be missed.[25] This approach has been frequently used in epidemiologic studies on fatty liver as there is no reasonable alternative.[26] The definition of NASH in our study is even more "presumed" as it is well known that a single increased ALT level is not a good indicator for NASH.[27] Nevertheless, in the lack of better options, increased ALT has been previously used as a marker for NASH.[28,29]

It should also be mentioned that the power of our study was not enough to prove the increased benefit among NASH participants vs non-NASH, although our findings did provide some indication that this may be the case.

We should caution that although the analysis of the consenting group is more sensitive as it excludes non-consenting participants from the original randomized population, there is a significant imbalance among baseline characteristics between the arms of this group and there is an increased risk of bias.

Conclusion

This is the first study that reports the effects of a polypill in participants with fatty liver or NASH. The benefits observed among subjects consenting to take polypill are consistent with our previous trial in people with unknown liver state and, taken together, our two trials reinforce each other and indicate that polypill is useful in people with and without fatty liver and NASH. It is not necessary to evaluate the state of the liver by ultrasound, liver stiffness level, or liver enzyme levels before starting polypill. In addition, our study indicates that polypill can reduce ALT levels in individuals with fatty liver and increased ALT.

Individuals with fatty liver and NASH are more likely to develop CVD. We do not have an effective medical treatment for the liver but preventing CVD, the main cause of death in this group, is an important management objective.

Funding:

The work was supported by the Barakat Foundation, Alborz Darou, and Tehran University of Medical Sciences. The Golestan Cohort Study is supported by Cancer Research UK [grant no. C20/A5860], Tehran University of Medical Sciences [grant no 81/15], and the International Agency for Research on Cancer (IARC). TM is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration (ARC) West Midlands. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. None of the funders were involved in any part of the study including design, data collection, statistical analysis or decision to publish.

Acknowledgements:

We would like to thank Karla Hemming who provided advice about analysis at the early stages of the study (after randomization) and commented on the final draft before submission for publication. We also thank Hamid Reza Jamshidi from the Barakat Foundation, Behrooz Abaie from the Digestive Disease Research Institute of Tehran University of Medical Sciences (Tehran, Iran), Golestan Cohort Study (GCS) center staff, Golestan University of Medical Sciences (Gorgan, Iran), and the chiefs of the Gonbad health districts for their assistance and support. We also thank the GCS participants who participated in this trial.

Data Availability Statement:

Individual de-identified data is available after request through emailing the corresponding author subject to the approval of the trial management team. Researchers might be required to submit a formal request.

Disclosures:

None to declare

Author Contributions:

RM, KKC, TM, and SM helped in designing the study. HP, SM, MK, and EJ helped in study administration and supervision. ARR and ASK performed and interpreted radiologic studies. Statistical analysis was performed by MS and EJ. The first draft was prepared by SM, MS, and EJ. All authors read and approved the final manuscript.

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Figure Legends:

Figure 1: Participant flow