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Gastroenterology (December 2021, Vol. 161, No. 6)

Parallel-Group Controlled Trial of Surgery Versus Chemoradiotherapy in Patients With Stage I Esophageal Squamous Cell Carcinoma

Ken Kato, Yoshinori Ito, Isao Nozaki, Hiroyuki Daiko, Takashi Kojima, Masahiko Yano, Masaki Ueno, Satoru Nakagawa, Masakazu Takagi, Shigeru Tsunoda, Tetsuya Abe, Tetsu Nakamura, Morihito Okada, Yasushi Toh, Yuichi Shibuya, Seiichiro Yamamoto, Hiroshi Katayama, Kenichi Nakamura, Yuko Kitagawa, Japan Esophageal Oncology Group of the Japan Clinical Oncology Group

Gastroenterology. 2021 Dec;161(6):1878-1886.e2. doi: 10.1053/j.gastro.2021.08.007.

https://www.gastrojournal.org/article/S0016-5085(21)03352-7/fulltext

Background & aims:
Surgery is the standard of care for T1bN0M0 esophageal squamous cell carcinoma (ESCC), whereas chemoradiotherapy (CRT) is a treatment option. This trial aimed to investigate the noninferiority of CRT relative to surgery for T1bN0M0 ESCC.

Methods:
Clinical T1bN0M0 ESCC patients were eligible for enrollment in this prospective nonrandomized controlled study of surgery versus CRT. The primary endpoint was overall survival, which was determined using inverse probability weighting with propensity scoring. Surgery consisted of an esophagectomy with 2- or 3-field lymph node dissection. CRT consisted of 2 courses of 5-fluorouracil (700 mg/m2) on days 1-4 and cisplatin (70 mg/m2) on day 1 every 4 weeks with concurrent radiation (60 Gy).

Results:
From December 20, 2006 to February 5, 2013, a total of 368 patients were enrolled in the nonrandomized portion of the study. The patient characteristics in surgery arm and CRT arm, respectively, were as follows: median age, 62 and 65 years; proportion of males, 82.8% and 88.1%; and proportion of performance status 0, 99.5% and 98.1%. Comparisons were made using the nonrandomized groups. The 5-year overall survival rate was 86.5% in the surgery arm and 85.5% in the CRT arm (adjusted hazard ratio, 1.05; 95% confidence interval, 0.67-1.64 [<1.78]). The complete response rate in the CRT arm was 87.3% (95% confidence interval, 81.1-92.1). The 5-year progression-free survival rate was 81.7% in the surgery arm and 71.6% in the CRT arm. Treatment-related deaths occurred in 2 patients in the surgery arm and none in the CRT arm.

Conclusions:
CRT is noninferior to surgery and should be considered for the treatment of T1bN0M0 ESCC.

BACK

Prevalence of Primary Sclerosing Cholangitis in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis

Brigida Barberio,Davide Massimi,Nora Cazzagon,Fabiana Zingone,Alexander C. Ford,Edoardo V. Savarino

Gastroenterology 2021;161(6):1865-1877.

https://www.gastrojournal.org/article/S0016-5085(21)03412-0/fulltext

Background & Aims
Although the association between inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC) is well recognized, uncertainties remain about the magnitude of this problem. We conducted a systematic review and meta-analysis assessing prevalence of PSC in IBD to investigate whether type of IBD, how presence of PSC was defined, sex, disease extent or location, time period, or geographic location influenced prevalence.

Methods
Medline, Embase, and Embase Classic were searched (from inception to April 10, 2021) to identify observational studies recruiting ≥50 adult patients with IBD and reporting prevalence of PSC. Data were extracted, and pooled prevalence, odds ratios (ORs), and 95% confidence intervals (CIs) calculated.

Results
Of 1204 citations, 64 studies were eligible, containing 776,700 patients. Overall, pooled prevalence of PSC in IBD was 2.16%; it was highest in South America and lowest in Southeast Asia. Pooled prevalences in patients with ulcerative colitis (UC), Crohn's disease (CD), and IBD-unclassified were 2.47%, 0.96%, and 5.01%, respectively. Pooled prevalence was significantly higher in UC versus CD (OR 1.69, 95% CI 1.24–2.29). In subgroup analyses according to method used to define presence of PSC, the highest prevalence was 2.88% in studies performing both liver biochemistry and endoscopic retrograde/magnetic resonance cholangiopancreatography and the lowest was 1.79% in studies using a clinical diagnosis. Prevalence was generally higher in men, patients with more extensive, compared with left-side, UC or ileocolonic or colonic, compared with ileal, CD.

Conclusions
Our findings provide the first pooled estimates of the burden of PSC in IBD, as well as potential risk factors, which may be important in establishing a prompt diagnosis and initiating appropriate surveillance for relevant gastrointestinal malignancies.

BACK

Regular Use of Proton Pump Inhibitor and the Risk of Inflammatory Bowel Disease: Pooled Analysis of 3 Prospective Cohorts

Bin Xia, Man Yang, Long H. Nguyen, Qiangsheng He, Jie Zhen, Yuanyuan Yu, Mengyang Di, Xiwen Qin, Kuiqing Lu, Zi Chong Kuo, Yulon

Gastroenterology 2021;161(6):1842-1852.

https://www.gastrojournal.org/article/S0016-5085(21)03350-3/fulltext

Background & Aims
Proton pump inhibitors (PPIs) have a major impact on gut microbiome and immune function, which in turn, may increase the risk of inflammatory bowel disease (IBD). Our aim in this study was to evaluate PPI use and subsequent risk of IBD and subtypes (ie, Crohn's disease and ulcerative colitis).

Methods
This was a pooled analysis of the Nurses' Health Study (NHS, n = 82,869), NHS II (n = 95,141), and UK Biobank (n = 469,397). We included participants with information on personal use of PPIs and free of IBD or cancer at baseline. We evaluated hazard ratios and 95% confidence intervals (CIs) with Cox regression adjusting for lifestyle factors, PPI indications, comorbidities, and other medications.

Results
We documented 271 cases of IBD (median follow-up, 12 years) in the pooled NHS cohorts and 1419 cases (median follow-up, 8.1 years) in the UK Biobank. For both pooled NHS cohorts and UK Biobank, regular use of PPIs consistently showed a significantly positive association with IBD, Crohn's disease, and ulcerative colitis risk. Combined analyses of 3 cohorts showed that regular PPI users had an increased risk of IBD as compared with nonusers (hazard ratio, 1.42; 95% CI, 1.22–1.65; number needed to harm, 3770; 95% CI, 3668–4369). Direct comparison with H2 receptor antagonist, a less potent acid suppressor, showed that PPI use was also associated with higher IBD risk (hazard ratio, 1.38; 95% CI, 1.16–1.65).

Conclusions
Regular use of PPIs was associated with an increased risk of IBD and its subtypes. The findings should be interpreted with caution because the absolute risk was low and the clinical benefits of PPIs are substantial.

BACK

Results of Early Transplantation for Alcohol-Related Cirrhosis: Integrated Addiction Treatment With Low Rate of Relapse

Lauren Carrique, Jill Quance, Adrienne Tan, Susan Abbey, Isabel Sales, Les Lilly, Mamatha Bhat, Zita Galvin, Mark Cattral, Anand Ghanekar, Ian McGilvray, Trevor Reichman, Gonzalo Sapisochin, Blayne Sayed, Markus Selzner, Marie-Josée Lynch §, Nazia Selzner §

Gastroenterology. 2021 Dec;161(6):1896-1906.

https://www.gastrojournal.org/article/S0016-5085(21)03342-4/fulltext

Background & Aims
In 2018, our team initiated a prospective pilot program to challenge the paradigm of the “6-month rule” of abstinence for patients with alcohol-related liver disease (ALD) requiring transplant. Our pilot involved an in-depth examination of patients’ alcohol use, social support, and psychiatric comorbidity, as well as the provision of pre- and post-transplantation addiction treatment.

Methods
Patients with ALD were assessed for inclusion in the pilot by a multidisciplinary team. Relapse prevention therapy was provided directly to all patients deemed to meet the program’s inclusion criteria. Random biomarker testing for alcohol was used pre and post transplantation.

Results
We received 703 referrals from May 1, 2018 to October 31, 2020. After fulfilling the program’s criteria, 101 patients (14%) were listed for transplantation and 44 (6.2%) received transplants. There were no significant differences in survival rates between those receiving transplants through the pilot program compared with a control group with more than 6 months of abstinence ($P = .07$). Three patients returned to alcohol use during an average post-transplantation follow-up period of 339 days. In a multivariate analysis, younger age and lower Model for End-Stage Liver Disease scores at listing were associated with an increased likelihood of a return to alcohol use ($P < .05$); length of abstinence was not a predictor.

Conclusions
Our prospective program provided direct monitoring and relapse prevention treatment for patients with ALD and with less than 6 months of abstinence and resulted in a reduction of post-transplantation return to drinking. This pilot study provides a framework for the future of more equitable transplant care.

BACK

GUT (December 2021, Vol. 70, No. 12)

Colorectal cancer risk following polypectomy in a multicentre, retrospective, cohort study: an evaluation of the 2020 UK post-polypectomy surveillance guidelines

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Gut. 2021 Dec;70(12):2307-2320. doi: 10.1136/gutjnl-2020-323411. Epub 2021 Mar 5

https://gut.bmj.com/content/gutjnl/70/12/2307.full.pdf

Objective:
Colonoscopy surveillance aims to reduce colorectal cancer (CRC) incidence after polypectomy. The 2020 UK guidelines recommend surveillance at 3 years for 'high-risk' patients with ≥2 premalignant polyps (PMPs), of which ≥1 is 'advanced' (serrated polyp (or adenoma) ≥10 mm or with (high-grade) dysplasia); ≥5 PMPs; or ≥1 non-pedunculated polyp ≥20 mm; 'low-risk' patients without these findings are instead encouraged to participate in population-based CRC screening. We examined the appropriateness of these risk classification criteria and recommendations.

Design:
Retrospective analysis of patients who underwent colonoscopy and polypectomy mostly between 2000 and 2010 at 17 UK hospitals, followed-up through 2017. We examined CRC incidence by baseline characteristics, risk group and number of surveillance visits using Cox regression, and compared incidence with that in the general population using standardised incidence ratios (SIRs).

Results:
Among 21 318 patients, 368 CRCs occurred during follow-up (median: 10.1 years). Baseline CRC risk factors included age ≥55 years, ≥2 PMPs, adenomas with tubulovillous/villous/unknown histology or high-grade dysplasia, proximal polyps and a baseline visit spanning 2-90 days. Compared with the general population, CRC incidence without surveillance was higher among those with adenomas with high-grade dysplasia (SIR 1.74, 95% CI 1.21 to 2.42) or ≥2 PMPs, of which ≥1 was advanced (1.39, 1.09 to 1.75). For low-risk (71%) and high-risk (29%) patients, SIRs without surveillance were 0.75 (95% CI 0.63 to 0.88) and 1.30 (1.03 to 1.62), respectively; for high-risk patients after first surveillance, the SIR was 1.22 (0.91 to 1.60).

Conclusion:
These guidelines accurately classify post-polypectomy patients into those at high risk, for whom one surveillance colonoscopy appears appropriate, and those at low risk who can be managed by non-invasive screening.

BACK

Long-term effectiveness of faecal immunochemical test screening for proximal and distal colorectal cancers

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Gut. 2021 Dec;70(12):2321-2329.

https://gut.bmj.com/content/gutjnl/70/12/2321.full.pdf

Objective:
To measure the effects of faecal immunochemical test (FIT) for colorectal cancer (CRC) screening on overall and site-specific long-term effectiveness of population-based organised service screening.

Design:
A prospective cohort study of Taiwanese nationwide biennial FIT screening was performed. A total of 5 417 699 eligible subjects were invited to attend screening from 2004 through 2009 and were followed up until 2014. We estimated the adjusted relative rates (aRRs) on the effectiveness of reducing advanced-stage CRC (stage II+) and CRC death by Bayesian Poisson regression models with the full adjustment for a cascade of self-selection factors (including the screening rate and the colonoscopy rate) and the completeness of colonoscopy together with demographic features.

Results:
FIT screening (exposed vs unexposed) reduced the incidence of advanced-stage CRC (48.4 vs 75.7 per 100 000) and mortality (20.3 vs 41.3 per 100 000). Statistically significant reductions of both incidence of advanced-stage CRCs (aRR=0.66, 95% CI 0.63 to 0.70) and deaths from CRC (aRR=0.60, 95% CI 0.57 to 0.64) were noted. FIT screening was more effective in reducing distal advanced-stage CRCs (aRR=0.61, 95% CI 0.58 to 0.64) and CRC mortality (aRR=0.56, 95% CI 0.53 to 0.69) than proximal advanced CRCs (aRR=0.84, 95% CI 0.77 to 0.92) and CRC mortality (aRR=0.72, 95% CI 0.66 to 0.80).

Conclusion:
A large-scale population-based biennial FIT screening demonstrates 34% significant reduction of advanced-stage CRCs and 40% reduction of death from CRC with larger long-term effectiveness in the distal colon than the proximal colon. Our findings provide a strong and consistent evidence-based policy for supporting a sustainable population-based FIT organised service screening worldwide. The disparity of site-specific long-term effectiveness also provides an insight into the remedy for lower effectiveness of FIT screening in the proximal colon.

BACK

Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women

Jinhee Hur, Ebunoluwa Otegbeye, Hee-Kyung Joh, Katharina Nimptsch, Kimmie Ng, Shuji Ogino, Jeffrey A Meyerhardt, Andrew T Chan, Walter C Willett, Kana Wu[#], Edward Giovannucci[#], Yin Cao[#]

Gut. 2021 Dec;70(12):2330-2336.

https://gut.bmj.com/content/gutjnl/70/12/2330.full.pdf

Objective:
Sugar-sweetened beverage (SSB) consumption had substantially increased across successive US birth cohorts until 2000, and adolescents and young adults under age 50 years have the highest consumption. However, the link between SSBs and early-onset colorectal cancer (EO-CRC) remains unexamined.

Design:
In the Nurses' Health Study II (1991-2015), we prospectively investigated the association of SSB intake in adulthood and adolescence with EO-CRC risk among 95 464 women who had reported adulthood beverage intake using validated food frequency questionnaires (FFQs) every 4 years. A subset of 41 272 participants reported beverage intake at age 13-18 years using a validated high school-FFQ in 1998. Cox proportional hazards models were used to estimate relative risks (RRs) with 95% CIs.

Results:
We documented 109 EO-CRC cases. Compared with individuals who consumed <1 serving/week of SSBs in adulthood, women who consumed ≥2 servings/day had a more than doubled risk of EO-CRC (RR 2.18; 95% CI 1.10 to 4.35; ptrend=0.02), with a 16% higher risk (RR 1.16; 95% CI 1.00 to 1.36) per serving/day increase. Each serving/day increment of SSB intake at age 13-18 years was associated with a 32% higher risk of EO-CRC (RR 1.32; 95% CI 1.00 to 1.75). Replacing each serving/day of adulthood SSB intake with that of artificially sweetened beverages, coffee, reduced fat milk or total milk was associated with a 17%-36% lower risk of EO-CRC.

Conclusion:
Higher SSB intake in adulthood and adolescence was associated with a higher risk of EO-CRC among women. Reduction of SSB consumption among adolescents and young adults may serve as a potential strategy to alleviate the growing burden of EO-CRC.

BACK

Synbindin restrains proinflammatory macrophage activation against microbiota and mucosal inflammation during colitis

Luoyan Ai, Yimeng Ren, Mingming Zhu, Shiyuan Lu, Yun Qian, Zhaofei Chen, Antao Xu

Gut 2021;70(12): 2261-2272.

https://gut.bmj.com/content/70/12/2261

Objective As a canonical membrane tethering factor, the function of synbindin has been expanding and indicated in immune response. Here, we investigated the role of synbindin in the regulation of toll-like receptor 4 (TLR4) signalling and macrophage response to microbiota during colitis.

Design Three distinct mouse models allowing global, myeloid-specific or intestinal epithelial cell-specific synbindin heterozygous deletion were constructed and applied to reveal the function of synbindin during dextran sodium sulfate (DSS) colitis. Effects of synbindin on TLR4 signalling and macrophage activation in response to bacterial lipopolysaccharide (LPS) or Fusobacterium nucleatum were evaluated. The colocalisation and interaction between synbindin and Rab7b were determined by immunofluorescence and coimmunoprecipitation. Synbindin expression in circulating monocytes and intestinal mucosal macrophages of patients with active IBD was detected.

Results Global synbindin haploinsufficiency greatly exacerbated DSS-induced intestinal inflammation. The increased susceptibility to DSS was abolished by gut microbiota depletion, while phenocopied by specific synbindin heterozygous deletion in myeloid cells rather than intestinal epithelial cells. Profoundly aberrant proinflammatory gene signatures and excessive TLR4 signalling were observed in macrophages with synbindin interference in response to bacterial LPS or Fusobacterium nucleatum. Synbindin was significantly increased in intestinal mucosal macrophages and circulating monocytes from both mice with DSS colitis and patients with active IBD. Interleukin 23 and granulocyte-macrophage colony-stimulating factor were identified to induce synbindin expression. Mechanistic characterisation indicated that synbindin colocalised and directly interacted with Rab7b, which coordinated the endosomal degradation pathway of TLR4 for signalling termination.

Conclusion Synbindin was a key regulator of TLR4 signalling and restrained the proinflammatory macrophage activation against microbiota during colitis.

BACK

Whole exome HBV DNA integration is independent of the intrahepatic HBV reservoir in HBeAg-negative chronic hepatitis B

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Gut 2021;70(12):2337-2348.

https://gut.bmj.com/content/70/12/2337

Objective The involvement of HBV DNA integration in promoting hepatocarcinogenesis and the extent to which the intrahepatic HBV reservoir modulates liver disease progression remains poorly understood. We examined the intrahepatic HBV reservoir, the occurrence of HBV DNA integration and its impact on the hepatocyte transcriptome in hepatitis B ‘e’ antigen (HBeAg)-negative chronic hepatitis B (CHB).

Design Liver tissue from 84 HBeAg-negative patients with CHB with low (n=12), moderate (n=25) and high (n=47) serum HBV DNA was analysed. Covalently closed circular DNA (cccDNA), pregenomic RNA (pgRNA) were evaluated by quantitative PCR, whole exome and transcriptome sequencing was performed by Illumina, and the burden of HBV DNA integrations was evaluated by digital droplet PCR.

Results Patients with low and moderate serum HBV DNA displayed comparable intrahepatic cccDNA and pgRNA, significantly lower than in patients with high HBV DNA, while hepatitis B core-related antigen correlated strongly with the intrahepatic HBV reservoir, reflecting cccDNA quantity. Whole exome integration was detected in a significant number of patients (55.6%, 14.3% and 25% in high, moderate and low viraemic patients, respectively), at a frequency ranging from 0.5 to 157 integrations/1000 hepatocytes. Hepatitis B surface antigen >5000 IU/mL predicted integration within the exome and these integrations localised in genes involved in hepatocarcinogenesis, regulation of lipid/drug metabolism and antiviral/inflammatory responses. Transcript levels of specific genes, including the proto-oncogene hRAS, were higher in patients with HBV DNA integration, supporting an underlying oncogenic risk in patients with low-level to moderate-level viraemia.

Conclusion HBV DNA integration occurs across all HBeAg-negative patients with CHB, including those with a limited HBV reservoir; localising in genes involved in carcinogenesis and altering the hepatocyte transcriptome.

BACK

Lancet Gastroenterology and Hepatology (December 2021, Vol. 6, No. 12)

Comparative efficacy and safety of biologic therapies for moderate-to-severe Crohn's disease: a systematic review and network meta-analysis

Siddharth Singh,M Hassan Murad,Mathurin Fumery,Rocio Sedano,Vipul Jairath,Remo Panaccione,William J Sandborn,Christopher Ma

The Lancet Gastroenterology & Hepatology 6(12):1002-1014

https://www.thelancet.com/journals/langas/article/PIIS2468-1253(21)00312-5/fulltext

Background Data are needed to inform the positioning of biologic therapy in the treatment of moderate-to-severe Crohn's disease, both first line and after previous biologic exposure. We aimed to assess the comparative efficacy and safety of biologics in patients with Crohn's disease.

Methods We did a systematic review and network meta-analysis of phase 2 and phase 3 randomised controlled trials done in adults (≥18 years) with moderate-to-severe Crohn's disease (Crohn's Disease Activity Index [CDAI] 220–450) treated with tumour necrosis factor (TNF) antagonists, anti-integrin, anti-interleukin (IL)-12 and IL-23p40, or anti-IL23p19 agents, either alone or in combination with immunosuppressants, as their first-line biologic or after previous biologic exposure, compared with placebo or an active comparator. The minimum duration of therapy was 14 days for trials reporting induction of remission in active disease and 22 weeks in trials reporting maintenance of remission. We searched Medline, EMBASE, the Cochrane CENTRAL Register of Controlled Trials, conference proceedings, trial registries, and unpublished data from inception to June 3, 2021, without any language restrictions. Summary estimates of the primary and secondary outcomes were extracted from the published reports; individual patient-level data were not sought. The primary endpoint was induction of clinical remission in patients with active disease (CDAI <150) and maintenance of remission in patients with response to induction therapy, with data extracted from published reports. A network meta-analysis with multivariate consistency model random-effects meta-regression was done, with rankings based on surface under the cumulative ranking curve (SUCRA) values.

Findings The search strategy yielded 18 382 citations, of which 31 trials were eligible for inclusion. On the basis of 15 randomised controlled trials including 2931 biologic-naive patients, infliximab monotherapy (odds ratio [OR] 4·53 [95% CI 1·49–13·79]), infliximab combined with azathioprine (7·49 [2·04–27·49]), adalimumab (3·01 [1·25–7·27]), and ustekinumab (2·63 [1·10–6·28]) were associated with significantly higher odds of inducing remission compared to certolizumab pegol (all moderate confidence); infliximab and azathioprine combination therapy was also associated with significantly higher odds of inducing remission than vedolizumab (3·76 [1·01–14·03]; low confidence). On the basis of ten randomised controlled trials including 2479 patients with previous biologic exposure, adalimumab after loss of response to infliximab (OR 2·82 [95% CI 1·20–6·62]; low confidence), and risankizumab (2·10 [1·12–3·92]; moderate confidence), were associated with higher odds of inducing remission than vedolizumab. No differences between active interventions were observed in maintenance trials. Most trials were at low or uncertain risk of bias.

Interpretation Although biologic treatment choices in patients with moderate-to-severe Crohn's disease must be individualised for each patient, this analysis suggests that either infliximab with azathioprine or adalimumab might be preferred as a first-line therapy, and adalimumab (after infliximab loss of response) or risankizumab might be preferred as a second-line therapy, for induction of clinical remission.

BACK

Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery (UPGRADE): a multicentre, double-blind, randomised, placebo-controlled superiority trial

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The Lancet Gastroenterology and Hepatology. 2021 Dec;6(12):993-1001.

https://www.thelancet.com/journals/langas/article/PIIS2468-1253(21)00301-0/fulltext

Background Rapid weight loss is a major risk factor for the formation of cholesterol gallstones. Consequently, patients with morbid obesity undergoing bariatric surgery frequently develop symptomatic gallstone disease. This trial assessed the efficacy of ursodeoxycholic acid versus placebo for the prevention of symptomatic gallstone disease after bariatric surgery.

Methods This multicentre, double-blind, randomised, placebo-controlled superiority trial enrolled patients with an intact gallbladder scheduled for laparoscopic Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy in three hospitals in the Netherlands. Patients were randomly assigned (1:1) by a web-based randomisation module to receive 900 mg ursodeoxycholic acid daily for 6 months or matched placebo. Randomisation was stratified by the presence of asymptomatic gallstones at baseline and type of surgery. Patients, clinicians, and study staff were masked to treatment allocation. The primary endpoint was symptomatic gallstone disease within 24 months, assessed in the modified intention-to-treat population (all randomly assigned eligible patients with any post-randomisation measurement). Prespecified subgroup analyses were done based on the stratification groups. Safety was assessed in all patients who took at least one dose of the study drug. This trial is registered with the Netherlands Trial Register, NL5954.

Findings Between Jan 11, 2017, and Oct 22, 2018, 985 patients were randomly assigned to receive either ursodeoxycholic acid (n=492) or placebo (n=493). 967 patients were included in the modified intention-to-treat population, of whom 959 had data available for primary endpoint assessment. 189 (20%) patients had asymptomatic gallstones at baseline and 78 (8%) received a sleeve gastrectomy. Symptomatic gallstone disease occurred in 31 (6·5%) of 475 patients in the ursodeoxycholic acid group and in 47 (9·7%) of 484 patients in the placebo group (relative risk 0·67, 95% CI 0·43–1·04, p=0·071). Logistic regression showed a significant interaction between ursodeoxycholic acid and the presence of asymptomatic gallstones at baseline (p=0·046), with an effect of ursodeoxycholic acid in patients without (0·47, 0·27–0·84, p=0·0081), and no effect in patients with asymptomatic gallstones at baseline (1·22, 0·61–2·47, p=0·57). The effect was stronger in patients without gallstones at baseline undergoing RYGB (0·37, 0·20–0·71, p=0·0016), whereas the subgroup of patients undergoing sleeve gastrectomy was too small to draw clear conclusions. Adverse events were rare. In the ursodeoxycholic acid group, diarrhoea occurred in four (0·9%) of 444 patients and skin rash in two (0·5%) patients. In the placebo group, diarrhoea occurred in two (0·4%) of 453 patients and skin rash in two (0·4%) patients. The total number of serious adverse events did not significantly differ between the trial groups (75 [17%] in 444 patients in the ursodeoxycholic acid group and 102 [23%] in 453 patients in the placebo group). The most common serious adverse events were abdominal pain and internal hernia. No serious adverse event was attributed to the study drug.

Interpretation Ursodeoxycholic acid prophylaxis did not significantly reduce the occurrence of symptomatic gallstone disease in all patients after bariatric surgery. In patients without gallstones before RYGB surgery, ursodeoxycholic acid treatment reduced the occurrence of symptomatic gallstone disease compared with placebo. Further research is needed to assess the efficacy of ursodeoxycholic acid after sleeve gastrectomy.

BACK

Hepatology (December 2021, Vol. 74, No. 6)

HBV Genotype: A Significant Risk Factor in Determining Which Patients With Chronic HBV Infection Should Undergo Surveillance for HCC: The Hepatitis B Alaska Study

Brian J. McMahon,Leisha D. Nolen,Mary Snowball,Chriss Homan,Susan Negus,Elena Roik,Philip R. Spradling,Dana Bruden

Hepatology. 2021 Dec;74(6):2965-2973.

https://doi.org/10.1002/hep.32065

Background & Aims
Information is limited regarding HBV genotype and the outcome of chronic HBV (CHB) infection. We examined the effect of HBV genotype on HCC occurrence in Alaska Native (AN) persons with CHB, where five HBV genotypes are found: A2, B6, C2, D, and F1.

Approach and Results
We calculated HCC incidence per 1,000 person-years of follow-up to determine which groups by age, sex, and genotype met current American Association for the Study of Liver Diseases (AASLD) HCC surveillance criteria. We used Poisson regression to compare HCC risk by genotype, age, sex, and Alaska region. Incidence of HCC was calculated using the sex-specific AASLD cutoff recommended for the Asian population of 50 years for women and 40 years for men. HCC screening was conducted semiannually using alpha-fetoprotein levels and abdominal ultrasound. Among 1,185 AN persons, median follow-up was 35.1 years; 667 (63%) were male. The HBV genotype distribution was 49% D, 18% F, 13% A, 6% C, 3% B, 0.1% H, and 12% undetermined. Sixty-three cases of HCC occurred. HCC incidence for genotype F was 5.73 per 1,000 person-years of follow-up, followed by 4.77 for C, 1.28 for A, 0.47 for D, and 0.00 for B. The HCC risk was higher for genotypes F (relative rate [RR], 12.7; 95% CI, 6.1-26.4), C (RR, 10.6; 95% CI, 4.3-26.0), and A (RR, 2.9; 95% CI, 1.0-8.0) compared to genotypes B and D. Among men < 40 years of age and women < 50 years of age, genotype F had the highest incidence (4.79/1,000 person-years).

Conclusions
HBV genotype was strongly associated with HCC. HBV genotype should be considered in risk factor stratification.

BACK

A Machine Learning Approach to Liver Histological Evaluation Predicts Clinically Significant Portal Hypertension in NASH Cirrhosis

Jaime Bosch,Chuhan Chung,Oscar M. Carrasco-Zevallos,Stephen A. Harrison,Manal F. Abdelmalek,Mitchell L. Shiffman,Don C. Rockey,Zahil Shanis,Dinkar Juyal,Harsha Pokkalla,Quang Huy Le,Murray Resnick,Michael Montalto,Andrew H. Beck,Ilan Wapinski,Ling Han,Catherine Jia,Zachary Goodman,Nezam Afdhal,Robert P. Myers,Arun J. Sanyal

Hepatology. 2021 Dec;74(6):3146-3160.

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Background & Aims
The hepatic venous pressure gradient (HVPG) is the standard for estimating portal pressure but requires expertise for interpretation. We hypothesized that HVPG could be extrapolated from liver histology using a machine learning (ML) algorithm.

Approach and Results
Patients with NASH with compensated cirrhosis from a phase 2b trial were included. HVPG and biopsies from baseline and weeks 48 and 96 were reviewed centrally, and biopsies evaluated with a convolutional neural network (PathAI, Boston, MA). Using trichrome-stained biopsies in the training set (n = 130), an ML model was developed to recognize fibrosis patterns associated with HVPG, and the resultant ML HVPG score was validated in a held-out test set (n = 88). Associations between the ML HVPG score with measured HVPG and liver-related events, and performance of the ML HVPG score for clinically significant portal hypertension (CSPH) (HVPG ≥ 10 mm Hg), were determined. The ML-HVPG score was more strongly correlated with HVPG than hepatic collagen by morphometry ($\rho = 0.47$ vs. $\rho = 0.28$; $P < 0.001$). The ML HVPG score differentiated patients with normal (0-5 mm Hg) and elevated (5.5-9.5 mm Hg) HVPG and CSPH (median: 1.51 vs. 1.93 vs. 2.60; all $P < 0.05$). The areas under receiver operating characteristic curve (AUROCs) (95% CI) of the ML-HVPG score for CSPH were 0.85 (0.80, 0.90) and 0.76 (0.68, 0.85) in the training and test sets, respectively. Discrimination of the ML-HVPG score for CSPH improved with the addition of a ML parameter for nodularity, Enhanced Liver Fibrosis, platelets, aspartate aminotransferase (AST), and bilirubin (AUROC in test set: 0.85; 95% CI: 0.78, 0.92). Although baseline ML-HVPG score was not prognostic, changes were predictive of clinical events (HR: 2.13; 95% CI: 1.26, 3.59) and associated with hemodynamic response and fibrosis improvement.

Conclusions
An ML model based on trichrome-stained liver biopsy slides can predict CSPH in patients with NASH with cirrhosis.

BACK

Test–Retest Reliability and Consistency of HVPG and Impact on Trial Design: A Study in 289 Patients from 20 Randomized Controlled Trials

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Background & Aims
Portal hypertension (PH) is a major driver for cirrhosis complications. Portal pressure is estimated in practice by the HVPG. The assessment of HVPG changes has been used for drug development in PH. This study aimed at quantifying the test–retest reliability and consistency of HVPG in the specific context of randomized controlled trials (RCTs) for the treatment of PH in cirrhosis and its impact on power calculations for trial design.

Approach and Results
We conducted a search of published RCTs in patients with cirrhosis reporting individual patient-level data of HVPG at baseline and after an intervention, which included a placebo or an untreated control arm. Baseline and follow-up HVPGs in the control groups were extracted after digitizing the plots. We assessed reliability and consistency and the potential impact of study characteristics. We retrieved a total of 289 before and after HVPG measurements in the placebo/untreated groups from 20 RCTs. The time span between the two HVPG measurements ranged between 20 minutes and 730 days. Pre-/post-HVPG variability was lower in studies including only compensated patients; therefore, modeled sample size calculations for trials in compensated cirrhosis were lower than for decompensated cirrhosis. A higher proportion of alcohol-associated cirrhosis and unicentric trials was associated with lower differences between baseline and follow-up measurements. The smallest detectable difference in an individual was 26% and 30% in compensated and decompensated patients, respectively.

Conclusions
The test–retest reliability of HVPG is overall excellent. Within-individual variance was higher in studies including higher proportions of decompensated patients. These findings should be taken into account when performing power analysis for trials based on the effects on HVPG or when considering HVPG as a tool to guide therapy of PH.

BACK

Journal of Hepatology (December 2021, Vol. 75, No. 6)

Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States

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Background & Aims
Recently, international experts proposed redefining non-alcoholic fatty liver disease (NAFLD) as metabolic dysfunction-associated fatty liver disease (MAFLD), based on modified criteria. It is suspected that outcomes such as mortality may differ for these clinical entities. We studied the impact of MAFLD and NAFLD on all-cause and cause-specific mortality in US adults.

Methods
We analyzed data from 7,761 participants in the Third National Health and Nutrition Examination Survey and their linked mortality through 2015. NAFLD was diagnosed by ultrasonographic evidence of hepatic steatosis without other known liver diseases. MAFLD was defined based on the criteria proposed by an international expert panel. The Cox proportional hazard model was used to study all-cause mortality and cause-specific mortality between MAFLD and NAFLD, with adjustments for known risk factors.

Results
During a median follow-up of 23 years, individuals with MAFLD had a 17% higher risk of all-cause mortality (hazard ratio [HR] 1.17; 95% CI 1.04-1.32). Furthermore, MAFLD was associated with a higher risk of cardiovascular mortality. NAFLD per se did not increase the risk of all-cause mortality. Individuals who met both definitions had a higher risk of all-cause mortality (HR 1.13, 95% CI 1.00-1.26), while individuals who met the definition for MAFLD but not NAFLD had a 1.7-fold higher risk of all-cause mortality (HR 1.66, 95% CI 1.19-2.32). Estimates for all-cause mortality were higher for those with advanced fibrosis and MAFLD than for those with advanced fibrosis and NAFLD.

Conclusion
In this US population-based study, MAFLD was associated with an increased risk of all-cause mortality, while NAFLD demonstrated no association with all-cause mortality after adjusting for metabolic risk factors.

Lay summary
Our findings provide further support for the idea that non-alcoholic fatty liver disease (NAFLD) is a part of a broader multi-system disease that also includes obesity, diabetes, high blood pressure, and high cholesterol. Therefore, re-defining NAFLD as metabolic dysfunction-associated fatty liver disease (MAFLD) may help improve our understanding of predictors that increase the risk of death.

BACK

Comparison of ADAPT, FIB-4 and APRI as non-invasive predictors of liver fibrosis and NASH within the CENTAUR screening population

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Background & Aims
The development of accurate non-invasive tests to detect and measure the extent of fibrosis and disease activity in patients with non-alcoholic steatohepatitis (NASH) – the progressive phenotype of non-alcoholic fatty liver disease (NAFLD) – is of great clinical importance. Herein, we aimed to validate the performance of PRO-C3 and ADAPT for the detection of moderate/severe fibrosis within the CENTAUR screening population.

Methods
PRO-C3 was assessed in plasma from the screening population of the phase IIb CENTAUR study (NCT02217475) in adults with NASH and liver fibrosis. The relation between PRO-C3 and histologic features of NASH was evaluated, as well as the demographics of patients with high and low levels of PRO-C3. The diagnostic ability of PRO-C3, as a standalone marker or incorporated into ADAPT, to identify patients with F≥2 and NASH was estimated using receiver-operating characteristic analysis and logistic regression models.

Results
A total of 517 individuals with matched biopsy and PRO-C3 measurements were included. Patients with PRO-C3 levels ≥20.2 ng/ml showed increased levels of insulin, HOMA-IR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and platelet count compared to patients with low PRO-C3 ($p < 0.05$). PRO-C3 increased stepwise with increasing liver fibrosis, lobular inflammation, hepatocyte ballooning, steatosis, and NAFLD activity score ($p < 0.05$), and could distinguish between NAFL and NASH ($p < 0.0001$). PRO-C3 was independently associated with fibrosis and NASH when adjusted for clinical confounders. ADAPT outperformed Fibrosis-4, AST-to-platelet ratio index, and AST/ALT ratio as a predictor of advanced fibrosis and NASH ($p < 0.001$).

Conclusions
PRO-C3 was associated with NAFLD activity score and fibrosis. ADAPT outperformed other non-invasive scores for detecting NASH. These data support the use of PRO-C3 and ADAPT as diagnostic tools to identify patients with NASH eligible for inclusion in clinical trials.

Lay summary
PRO-C3 is a serological biomarker associated with liver disease activity and fibrosis. Its performance for the detection of disease activity and fibrosis is improved when it is incorporated into the ADAPT score. Herein, we showed that ADAPT was better at selecting patients with non-alcoholic steatohepatitis for inclusion in clinical trials than other non-invasive scores.

BACK

Protease inhibitor-based direct-acting antivirals are associated with increased risk of aminotransferase elevations but not hepatic dysfunction or decompensation

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Background & Aims
Cases of acute liver injury (ALI) have been reported among chronic HCV-infected patients receiving protease inhibitor (PI)-based direct-acting antiviral (DAA) regimens, but no analyses have compared the risk of ALI in patients receiving PI- vs. non-PI-based DAAs. Thus, we compared the risk of 3 ALI outcomes between patients (by baseline Fibrosis-4 [FIB-4] group) receiving PI-based or non-PI-based DAAs.

Methods
We conducted a cohort study of 18,498 patients receiving PI-based DAA therapy (paritaprevir/ritonavir/ombitasvir±dasabuvir, elbasvir/grazoprevir, glecaprevir/pibrentasvir) matched 1:1 on propensity score to those receiving non-PI-based DAAs (sofosbuvir/ledipasvir, sofosbuvir/velpatasvir) in the 1945-1965 Veterans Birth Cohort (2014-2019). During exposure to DAA therapy, we determined development of: i) alanine aminotransferase (ALT) >200 U/L, ii) severe hepatic dysfunction (coagulopathy with hyperbilirubinemia), and iii) hepatic decompensation. We used Cox regression to determine hazard ratios (HRs) with 95% CIs for each ALI outcome within groups defined by baseline FIB-4 (≤3.25; >3.25).

Results
Among patients with baseline FIB-4 ≤3.25, those receiving PIs had a higher risk of ALT >200 U/L (HR 3.98; 95% CI 2.37-6.68), but not severe hepatic dysfunction (HR 0.67; 95% CI 0.19-2.39) or hepatic decompensation (HR 1.01; 95% CI 0.29-3.49), compared to those receiving non-PI-based regimens. For those with baseline FIB-4 >3.25, those receiving PIs had a higher risk of ALT >200 U/L (HR, 2.15; 95% CI 1.09-4.26), but not severe hepatic dysfunction (HR, 1.23 [0.64-2.38]) or hepatic decompensation (HR, 0.87; 95% CI 0.41-1.87), compared to those receiving non-PI-based regimens

Conclusions
While risk of incident ALT elevations was increased in those receiving PI-based DAAs in both FIB-4 groups, the risk of severe hepatic dysfunction and hepatic decompensation did not differ between patients receiving PI- or non-PI-based DAAs in either FIB-4 group.

Lay summary
Cases of liver injury have been reported among patients treated with protease inhibitor-based direct-acting antivirals for hepatitis C infection, but it is not clear if the risk of liver injury among people starting these drugs is increased compared to those starting non-protease inhibitor-based therapy. In this study, patients receiving protease inhibitor-based treatment had a higher risk of liver inflammation than those receiving a non-protease inhibitor-based treatment, regardless of the presence of pre-treatment advanced liver fibrosis/cirrhosis. However, the risk of severe liver dysfunction and decompensation were not higher for patients treated with protease inhibitor-based regimens.

BACK

Performance of the model for end-stage liver disease score for mortality prediction and the potential role of etiology

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Background & Aims
Although the discriminative ability of the model for end-stage liver disease (MELD) score is generally considered acceptable, its calibration is still unclear. In a validation study, we assessed the discriminative performance and calibration of 3 versions of the model: original MELD-TIPS, used to predict survival after transjugular intrahepatic portosystemic shunt (TIPS); classic MELD-Mayo; and MELD-UNOS, used by the United Network for Organ Sharing (UNOS). We also explored recalibrating and updating the model.

Methods
In total, 776 patients who underwent elective TIPS (TIPS cohort) and 445 unselected patients (non-TIPS cohort) were included. Three, 6 and 12-month mortality predictions were calculated by the 3 MELD versions: discrimination was assessed by c-statistics and calibration by comparing deciles of predicted and observed risks. Cox and Fine and Grey models were used for recalibration and prognostic analyses.

Results
In the TIPS/non-TIPS cohorts, the etiology of liver disease was viral in 402/188, alcoholic in 185/130, and non-alcoholic steatohepatitis in 65/33; mean follow-up±SD was 25±9/19±21 months; and the number of deaths at 3-6-12 months was 57-102-142/31-47-99, respectively. C-statistics ranged from 0.66 to 0.72 in TIPS and 0.66 to 0.76 in non-TIPS cohorts across prediction times and scores. A post hoc analysis revealed worse c-statistics in non-viral cirrhosis with more pronounced and significant worsening in the non-TIPS cohort. Calibration was acceptable with MELD-TIPS but largely unsatisfactory with MELD-Mayo and -UNOS whose performance improved much after recalibration. A prognostic analysis showed that age, albumin, and TIPS indication might be used to update the MELD.

Conclusion
In this validation study, the performance of the MELD score was largely unsatisfactory, particularly in non-viral cirrhosis. MELD recalibration and candidate variables for an update to the MELD score are proposed.

Lay summary
While the discriminative performance of the model for end-stage liver disease (MELD) score is credited to be fair to good, its calibration, the correspondence of observed to predicted mortality, is still unsettled. We found that application of 3 different versions of the MELD in 2 independent cirrhosis cohorts yielded largely imprecise mortality predictions particularly in non-viral cirrhosis. Thus, we propose a recalibration and suggest candidate variables for an update to the model.

BACK

Endoscopy (December 2021, Vol. 53, No. 12)

Evaluation of the effects of an artificial intelligence system on endoscopy quality and preliminary testing of its performance in detecting early gastric cancer: a randomized controlled trial

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Endoscopy 2021; 53(12): 1199-1207

https://www.thieme-connect.de/products/ejournals/html/10.1055/a-1350-5583

Background
Esophagogastroduodenoscopy (EGD) is a prerequisite for detecting upper gastrointestinal lesions especially early gastric cancer (EGC). An artificial intelligence system has been shown to monitor blind spots during EGD. In this study, we updated the system (ENDOANGEL), verified its effectiveness in improving endoscopy quality, and pretested its performance in detecting EGC in a multicenter randomized controlled trial.

Methods
ENDOANGEL was developed using deep convolutional neural networks and deep reinforcement learning. Patients undergoing EGD in five hospitals were randomly assigned to the ENDOANGEL-assisted group or to a control group without use of ENDOANGEL. The primary outcome was the number of blind spots. Secondary outcomes included performance of ENDOANGEL in predicting EGC in a clinical setting.

Results
1050 patients were randomized, and 498 and 504 patients in the ENDOANGEL and control groups, respectively, were analyzed. Compared with the control group, the ENDOANGEL group had fewer blind spots (mean 5.38 [standard deviation (SD) 4.32] vs. 9.82 [SD 4.98]; $P<0.001$) and longer inspection time (5.40 [SD 3.82] vs. 4.38 [SD 3.91] minutes; $P<0.001$). In the ENDOANGEL group, 196 gastric lesions with pathological results were identified. ENDOANGEL correctly predicted all three EGCs (one mucosal carcinoma and two high grade neoplasias) and two advanced gastric cancers, with a per-lesion accuracy of 84.7%, sensitivity of 100%, and specificity of 84.3% for detecting gastric cancer.

Conclusions
In this multicenter study, ENDOANGEL was an effective and robust system to improve the quality of EGD and has the potential to detect EGC in real time.

BACK

The effect of train-the-colonoscopy-trainer course on colonoscopy quality indicators

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https://www.thieme-connect.de/products/ejournals/abstract/10.1055/a-1352-4583

Background
Systematic training in colonoscopy is highly recommended; however, we have limited knowledge of the effects of “training-the-colonoscopy-trainer” (TCT) courses. Using a national quality register on colonoscopy performance, we aimed to evaluate the effects of TCT participation on defined quality indicators.

Methods
This observational study compared quality indicators (pain, cecal intubation, and polyp detection) between centers participating versus not participating in a TCT course. Nonparticipating centers were assigned a pseudoparticipating year to match their participating counterparts. Results were compared between first year after and the year before TCT (pseudo)participation. Time trends up to 5 years after TCT (pseudo)participation were also compared. Generalized estimating equation models, adjusted for age, sex, and bowel cleansing, were used.

Results
11 participating and 11 nonparticipating centers contributed 18 555 and 10 730 colonoscopies, respectively. In participating centers, there was a significant increase in detection of polyps ≥5 mm, from 26.4% to 29.2% (P=0.035), and reduction in moderate/severe pain experienced by women, from 38.2% to 33.6% (P=0.043); no significant changes were found in nonparticipating centers. Over 5 years, 20 participating and 18 nonparticipating centers contributed 85 691 and 41 569 colonoscopies, respectively. In participating centers, polyp detection rate increased linearly (P=0.003), and pain decreased linearly in women (P=0.004). Nonparticipating centers did not show any significant time trend during the study period.

Conclusions
Participation in a TCT course improved polyp detection rates and reduced pain experienced by women. These effects were maintained during a 5-year follow-up.

BACK

The outcomes of emergency hospital admissions with non-malignant upper gastrointestinal bleeding in England between 2003 and 2015

James Rees, Felicity Evison, Jemma Mytton, Prashant Patel, Nigel Trudgill

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https://www.thieme-connect.de/products/ejournals/abstract/10.1055/a-1330-7118

Background
Upper gastrointestinal bleeding (UGIB) is a common medical emergency with significant mortality. Despite developments in endoscopic and clinical management, only minor improvements in outcomes have been reported.

Methods
This was a retrospective cohort study of patients with non-malignant UGIB emergency admissions in England between 2003 and 2015, using Hospital Episode Statistics. Multilevel logistic regression analysis examined the associations with mortality.

Results
242 796 patients with an UGIB admission were identified (58.8% men; median age 70 [interquartile range (IQR) 53–81]). Between 2003 and 2015, falls occurred in both 30-day mortality (7.5% to 7.0%; P<0.001) and age-standardized mortality (odds ratio (OR) 0.74, 95% confidence interval [CI] 0.69–0.80; P<0.001), including from variceal bleeding (OR 0.63, 95%CI 0.45–0.87; P<0.005). Increasing co-morbidity (Charlson score >5, OR 2.94, 95%CI 2.85–3.04; P<0.001), older age (>83 years, OR 6.50, 95%CI 6.09–6.94; P<0.001), variceal bleeding (OR 2.03, 95%CI 1.89–2.18; P<0.001), and a weekend admission (Sunday, OR 1.18, 95%CI 1.12–1.23; P<0.001) were associated with 30-day mortality. Of deaths at 30 days, 8.9% were from ischemic heart disease (IHD) and the cardiovascular age-standardized mortality rate following UGIB was high (IHD deaths within 1 year, 1188.4 [95%CI 1036.8–1353.8] per 100 000 men in 2003).

Conclusions
Between 2003 and 2015, 30-day mortality among emergency admissions with non-malignant UGIB fell by 0.5% to 7.0%. Mortality was higher among UGIB admissions at the weekend, with important implications for service provision. Patients with UGIB had a much greater risk of subsequently dying from cardiovascular disease and addressing this risk is a key management step in UGIB.

BACK