Gluten does not increase risk of myocardial infarction p 219

New tool can help select patients with stroke for intra-arterial treatment p 220

Elizabeth Loder: Getting strict with unregistered trials p 221

FDA required postapproval studies are inadequate p 222

**ORIGINAL RESEARCH** Prospective cohort study

Long term gluten consumption in adults without celiac disease and risk of coronary heart disease


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Find this at: http://dx.doi.org/10.1136/bmj.j1892

**Study question** Is long term consumption of dietary gluten associated with an increased risk of developing coronary heart disease?

**Methods** In this prospective cohort study of women in the Nurses’ Health Study (n=64 714) and men in the Health Professionals Follow-up Study (n=45 303), the exposure of interest was dietary gluten, measured by semiquantitative food frequency questionnaires that were administered in 1986 and updated every four years up to 2010. The primary outcome was coronary heart disease (fatal or non-fatal myocardial infarction).

**Study answer and limitations** The coronary heart disease incidence rate was 352 per 100 000 person years for participants in the lowest fifth of gluten intake and 277 events per 100 000 person years for those in the highest fifth. After adjustment for known risk factors, participants in the highest fifth of estimated gluten intake had a multivariable hazard ratio for coronary heart disease of 0.95 (95% confidence interval 0.88 to 1.02; P for trend=0.29). However, after additional adjustment for intake of refined grains (leaving the variance of gluten intake correlating with whole grain intake), estimated gluten consumption was associated with a lower risk of coronary heart disease (multivariate hazard ratio 0.85, 0.77 to 0.93; P for trend=0.002). A limitation of the study was that the food frequency questionnaires could not identify participants on a strictly gluten-free diet.

**What this study adds** Among male and female health professionals followed for more than 25 years, quantity of gluten consumption was not associated with coronary heart disease. A reduction in dietary gluten may result in reduced consumption of whole grains, which are associated with lower cardiovascular risk.

**Funding, competing interests, data sharing** See bmj.com.

<table>
<thead>
<tr>
<th>Variables</th>
<th>1 (lowest)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 (highest)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean; median (range) gluten intake (g/d)</td>
<td>2.6; 2.8 (0-3.4)</td>
<td>3.8; 3.8 (3.4-4.3)</td>
<td>4.7; 4.7 (4.3-5.1)</td>
<td>5.6; 5.6 (5.1-6.2)</td>
<td>7.5; 7.1 (6.2-26.7)</td>
<td>–</td>
</tr>
<tr>
<td>Nurses’ Health Study</td>
<td>2.6; 2.8 (0-3.4)</td>
<td>3.8; 3.8 (3.4-4.3)</td>
<td>4.7; 4.7 (4.3-5.1)</td>
<td>5.6; 5.6 (5.1-6.2)</td>
<td>7.5; 7.1 (6.2-26.7)</td>
<td>–</td>
</tr>
<tr>
<td>Health Professionals Follow-up Study</td>
<td>3.3; 3.5 (0-4.3)</td>
<td>4.9; 4.9 (4.3-5.5)</td>
<td>6.0; 6.0 (5.5-6.6)</td>
<td>7.3; 7.3 (6.6-8.1)</td>
<td>10.0; 9.4 (8.1-18.4)</td>
<td>–</td>
</tr>
<tr>
<td>Pooled results</td>
<td>352</td>
<td>273</td>
<td>286</td>
<td>257</td>
<td>277</td>
<td>–</td>
</tr>
<tr>
<td>No of events</td>
<td>1422</td>
<td>1238</td>
<td>1343</td>
<td>1227</td>
<td>1299</td>
<td>–</td>
</tr>
<tr>
<td>Incidence per 100 000 person years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Age adjusted HR (95% CI)</td>
<td>1.0 (reference)</td>
<td>0.83 (0.77 to 0.90)</td>
<td>0.89 (0.83 to 0.96)</td>
<td>0.81 (0.75 to 0.87)</td>
<td>0.87 (0.80 to 0.93)</td>
<td>0.001</td>
</tr>
<tr>
<td>Multivariable adjusted HR (95% CI)*</td>
<td>1.0 (reference)</td>
<td>0.90 (0.83 to 0.97)</td>
<td>0.98 (0.91 to 1.06)</td>
<td>0.91 (0.84 to 0.98)</td>
<td>0.98 (0.91 to 1.06)</td>
<td>0.81</td>
</tr>
<tr>
<td>Full model HR (95% CI)†</td>
<td>1.0 (reference)</td>
<td>0.88 (0.82 to 0.95)</td>
<td>0.96 (0.89 to 1.04)</td>
<td>0.88 (0.82 to 0.95)</td>
<td>0.95 (0.88 to 1.02)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

*HR=hazard ratio.

†See bmj.com for list of risk factors.
Selecting patients for endovascular treatment of stroke

Selection of patients for intra-arterial treatment for acute ischaemic stroke

Venema E, Mulder MJHL, Roozenbeek B, et al

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Find this at: http://dx.doi.org/10.1136/bmjj1710

Study question Can we improve the selection of patients with acute ischaemic stroke for intra-arterial treatment by predicting individual treatment benefit?

Methods The authors developed a multivariable prediction model using data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN, n=500). This model was validated using a subgroup of patients with a proved occlusion in the Interventional Management of Stroke III trial (IMS III, n=260). The authors performed ordinal logistic regression to predict the functional outcome and treatment benefit of individual patients. The primary outcome was the modified Rankin Scale (mRS) score at 90 days after stroke. Treatment benefit was defined as the difference between the predicted probability of good functional outcome (mRS score 0-2) with and without intra-arterial treatment. Variables were selected using univariable and multivariable selection steps (P<0.15).

Commentary New prediction tool will improve decision making at a critical time

Endovascular thrombectomy improves functional outcome in patients with severe stroke due to an occlusion of the internal carotid artery or proximal middle cerebral artery if the procedure is started within six hours from symptom onset. A recent meta-analysis found that, compared with standard treatment, for every 1000 patients undergoing endovascular thrombectomy in addition to standard medical treatment, 167 more will attain a good outcome. The benefit is greatest for patients treated in the earliest time windows.

In many countries, endovascular thrombectomy is the standard of care for eligible patients. But provision requires expertise and resources that are not always available. To improve access, regional systems of care have been reorganised to allow rapid identification and transfer of potential candidates to these centres (designated as comprehensive stroke centres in some jurisdictions). The transfer provides access to an effective treatment for patients who may not have otherwise received treatment but is costly for the health system, risky.

This study shows the importance of considering several clinical variables when making treatment decisions for patients, and inconvenient for their families. Even when patients are first seen at a comprehensive stroke centre, proceeding with endovascular thrombectomy incurs substantial opportunity costs because resources are potentially diverted from other patients. To maximise benefit and minimise both harm and costs, it is important to identify those patients who are most likely to respond and those for whom this treatment would be futile or harmful. In the linked paper, Venema and colleagues go some way to achieving this goal.

Eligibility decisions

Currently, clinicians make decisions about endovascular thrombectomy using a patient’s clinical and imaging findings to provide a qualitative estimate of the probability of a given outcome. At some centres, individual features such as age or specific imaging findings are used to determine eligibility. Venema and colleagues developed and validated a multivariable prediction model that combines baseline risks and 11 clinical and imaging features to estimate the absolute effect of treatment. The model was developed using data from the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) trial and validated in a subset of patients enrolled in the IMS-III (Interventional Management of Stroke III) trial.

The resulting model applies to most patients currently transferred to a comprehensive stroke centre because participants in MR CLEAN were identified with the most widely used imaging modalities (non-contrast computed tomography and computed tomography angiography) and, for the 90% of patients treated with intravenous alteplase, randomisation was done after the infusion was complete. The use of IMS-III data for validation improves the external validity of the model because the trials were done in different settings. In both cohorts the model performed moderately well to estimate the benefit of endovascular thrombectomy in individual patients. The authors provide an online calculator that may be used by clinicians considering endovascular thrombectomy once imaging is...
The persistent problem of unregistered clinical trials

In 2004 the International Committee of Medical Journal Editors (ICMJE) announced that clinical trials commencing after 1 July 2005 would be subject to a new trial registration policy. In order to be published in member journals, trials would have to be registered in an approved trial registry before enrollment of the first participant. The registry entries, in publicly accessible databases, would provide a reliable record of a trial’s existence and planned outcomes. The requirement for prospective trial registration was intended as a safeguard against well-documented and pervasive problems of selective reporting and non-publication of clinical trial results.

A third of trials from 2012 through 2014 were registered late

Things have improved dramatically since then, but we are nevertheless a long way from realising the full potential of trial registration. Unregistered and retrospectively registered trials continue to be published, especially by small journals whose editors do not uniformly embrace or understand the need for trial registration. Even the Committee on Publication Ethics takes a soft line on late trial registration, suggesting that “it is probably best to judge each paper on a case by case basis.” Perhaps such permissive attitudes explain why a recent analysis of data from the largest trial registry, Clinicaltrials.gov, shows that about a third of trials from 2012 through 2014 were registered late, defined as more than three months after their start.

What would it take to make unregistered or retrospectively registered clinical trials a thing of the past? One solution might be to treat them as the research equivalent of medical “never events.”

Never events

Like medical never events, unregistered clinical trials are “of concern to patients, policy makers, and healthcare professionals and providers.” They thwart a system designed to ensure the honest reporting of medical research. Also like medical never events, late or unregistered clinical trials are “clearly identifiable and measurable (and thus feasible to include in a reporting system).” Audits of various kinds can be undertaken to assess compliance with registration and outcome reporting.

Appropriate response

Finally, as with medical never events, late or nonexistent trial registration tells us “something fundamental about the quality, care, and safety processes in an organisation.” Attention to detail is the hallmark of good research. It is reasonable to wonder whether a research team unable to comply with registration requirements might have overlooked other vital details.

In the hospital world, never events trigger a harsh response. A similar approach could be used for non-registration. Funders and ethical approval bodies might make full payment or final approval of trials contingent on prospective registration. Journal editors should continue to refuse to publish such studies and notify institutional or company authorities of the problem when possible. Trial results can be publicly posted, for example on Clinicaltrials.gov or sponsor websites, and thus need not be lost to posterity even if no journal will publish them. Institutional discipline could take many forms, including additional oversight of subsequent research projects or requiring that such omissions be considered in decisions about academic promotion.

All parts of the research community must work together and make prospective registration of clinical trials a top priority. A main goal of the requirement for trial registration was to restore public trust in medical research. Trustworthy clinical trials = prospectively registered trials that faithfully report their prespecified outcomes. Unregistered clinical trials are serious, preventable events that should never happen—and must come first on any list of research never events.

Elizabeth Loder is head of research, The BMJ.
Conditional approval of medicines

ORIGINAL RESEARCH Systematic review

Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence

Pease AM, Krumholz HM, Downing NS, et al

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Study question Are adequate prospective controlled clinical studies published to prove the efficacy of novel drugs initially approved by the US Food and Drug Administration on the basis of limited evidence?

Methods The authors carried out a systematic review of the biomedical literature for 117 novel drugs originally approved by the FDA for 123 indications between 2005 and 2012. Study answer and limitations At a median of 5.5 years (interquartile range 3.4-8.2) after approval, 758 studies were published, none for 35.0% (43 of 123) of approved indications. The median number of postapproval studies was 1 (interquartile range 0-2) for indications approved on the basis of a single pivotal trial, 3 (1-8) for indications approved on the basis of pivotal trials that used surrogate markers of disease as primary endpoints, and 1 (0-2) for indications that met both criteria (single surrogate marker trial). The median aggregate number of patients enrolled was 90 (0-509), 533 (122-3633), and 38 (0-666), respectively. The proportion of approved indications with one or more randomised controlled double blind study using a clinical outcome for the primary endpoint that was published after approval and showed superior efficacy was 18.2% (6 of 33), 2.0% (1 of 49), and 4.9% (2 of 41), respectively. Study limitations included the inclusion of only English language articles published in journals indexed in Medline as at 31 December 2014.

What this study adds The quantity and quality of postapproval clinical evidence varied substantially for novel drugs first approved by the FDA on the basis of limited evidence, with few controlled studies published after approval that confirmed superior efficacy using clinical outcomes for the original FDA approved indication. Funding, competing interests, data sharing This project was supported in part by the Robert E Leet and Clara Guthrie Patterson Trust Awards Program in Clinical Research, Bank of America, NA, Trustee. See full article on bmj.com for competing interests. Requests for collected data and statistical code can be made to the corresponding author.

COMMENTARY The process fails to improve the evidence after early licensing

Like other expedited procedures for early marketing authorisation, conditional approval stems from the assumption that immediate availability of new drugs offers patients a benefit that outweighs the risks of limited clinical information. To some extent, this assumption applies to all licensed drugs, but early approval magnifies the need for “managing the unknown.”

Earlier this year, the European Medicines Agency reported its experience with conditional approval of new medicines. The report is an important step towards greater transparency and contributes useful data to help reflections on whether postmarketing commitments improve the value of new medicines by an average of four years. Any suggestion that early access to medicines without comprehensive data benefits patients should be supported by evidence. Even when manufacturers do eventually provide comprehensive clinical data, it can hardly be considered as ethically and clinically appropriate that patients and their doctors have been unaware of the benefit-risk profile of medicines they have been using for a long time. Regulatory processes should be designed first and foremost to establish the clinical value of new drugs, to satisfy the health needs of patients and the public. The EMA should require better evidence of safety and efficacy at the time of conditional approval, and insist on even more convincing data before full approval.

Find the full version with references at http://dx.doi.org/10.1136/bmj.2062

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See full article on bmj.com for author details

Rita Banzi rita.banzi@marionegri.it
Chiara Gerardi
Vittorio Bertele
Silvio Garattini
See bmj.com for author details