Editorial

The virtual patient – Estimating the health utility of aspirin in simulated populations

Aspirin (acetyl salicylic acid) is a cornerstone of secondary prevention in patients with cardiovascular (CV) risk and a prior ischemic event. Its application in patients with atrial fibrillation is still a matter of debate, [1,2] as is its value for primary prevention of myocardial ischemia and stroke in patients with CV risk factors [3]. Recent meta-analyses and randomised clinical trials (RCT) did not confirm the net benefit of aspirin determined in previous studies, while highlighting the elevated bleeding risk. One consideration in this context is that the average CV patients of today differ substantially from those of 20–30 years ago. They are often younger, with access to improved glucose-lowering and lipid-modifying agents, some of which, such as statins and renin-angiotensin system inhibitors, possess beneficial pleiotropic CV effects. All these factors may off-set the incremental benefit of aspirin. Another consideration is that the incidence of vascular events in the large recent trials ARRIVE, ASCEND and ASPREE was approximately half of the predicted incidence of 2–3% per year, so that these studies essentially evaluated aspirin in cohorts with very low risk, where the benefit of aspirin is unlikely to be unmasked compared to cohorts with at least moderate CV risk [4]. Thus there is a clear unmet need to estimate the global public health impact of aspirin in large-scale real-world settings, with an adequate baseline incidence of thrombotic events, accounting for background morbidities, disease state transition, comedications and treatment adherence. Another factor that needs consideration is the ability to reduce the risk of certain cancers, particularly colorectal cancer (CRC), [5]. CV disease increases the risk of cancer, [6] and modification of this association should be incorporated into the calculation of the net health utility of aspirin.

Meta-analyses provide a quantitative, systematic summary of all available evidence from multiple studies, for an overall estimate of the effect of a given intervention. The incorporation of data from many different studies vastly increases the number of cases and statistical power, enables generalization to larger populations, and provides an opportunity to identify variations between studies and the study cohorts, which may shed light on variability in terms of efficacy of the interventions. Conversely, the validity of *meta*-analyses is threatened by flaws or limitations of the considered studies, in terms of their heterogeneity of included populations, along with differences in design, conduct or analysis. Study size is a major source of inter-study heterogeneity, and the significance of small-study effects needs to be considered critically, as does the influence of selection and publication bias.

Demographic health models provide a complementary approach to estimate public-health outcomes. A simulated representative population can be modelled to assess the incremental impact of a given intervention, education or screening programme, accounting for transition between healthy and diseased states, prevalence rates and treatment duration. Because the number of states in a given model will increase exponentially with inclusion of all relevant or remotely relevant risk factors and exposure histories, elegant micro-simulation approaches have been developed and refined to model populations over time as they age and switch between disease and healthy states. Considerations for the design of static and dynamic study populations for modelling of chronic diseases have been comprehensively summaried elsewhere [7]. Micro-simulations have been applied for example to estimate the net public health costs of CV risk prevention, [8,9] or identify disease thresholds, where the benefits of interventions such as anti-platelet therapy will exceed the associated risk [10].

In this issue of the journal, Biccler and colleagues [11] now apply a micro-simulation model to assess the public-health impact of population-wide use of low-dose aspirin, weighing safety against benefit in terms of both CV risk reduction and prevention of CRC-associated mortality and morbidity. Two hypothetical cohorts of 1 million adults each aged either 50–59 years or 60–69 years were modelled using evidence-based parameters specific for the UK, and simulated as either off or on low-dose aspirin for up to 20 years. The authors carefully distinguish between those receiving aspirin for primary or secondary prevention, with indication for primary prevention based on the QRISK3 algorithm predicting a 10-year CV risk of at least 10%. In this way, baseline risk due to age, sex, smoking habit, body mass index, cholesterol levels and disease status such as diabetes, chronic renal disease or other inflammatory comorbidites, could be accounted for. Outcomes were reductions in fatal and non-fatal CV or CRC events vs. rates of intracranial haemorrhage and hospitalization or death due to gastrointestinal bleeding or symptomatic peptic ulcers. Since fatal peptic ulcers usually coincide with fatal gastrointestinal bleeds, the two entities were counted as a single event. The complex model design is comprehensively detailed in the supplement, clearly outlining how other confounding factors are taken into consideration, such as discontinuation, CRC screening or use of proton-pump inhibitors. Statin use was not incorporated into the model, which may have skewed the utility assessment in favour of aspirin, but this aspect is critically discussed by the authors with

reference to similar studies based on US data that did consider statin use.

The net finding of the simulation study is that in both age cohorts, the decrease in risk and number of fatal CV and CRC events outweighs the increase in fatal adverse events, irrespective of whether aspirin is indicated for primary or secondary prevention. The CV risk reduction was greater in the group requiring secondary prevention, in line with a higher risk burden. Safety events were comparable regardless of indication. The risk–benefit ratio for CRC was also comparable in those with indications for primary or secondary prevention. A critical parameter applied to the model is the uncertainty when the protective impact of aspirin manifests in terms of CRC risk. Adverse effects will typically follow early after initiation of treatment, while benefits in terms of risk reduction emerges in the longer term. For CRC risk, this lies between 1 and 5 years, with recent evidence for a suggestive benefit emerging after 6–10 years, and a clear protection evident after at least 10 years of aspirin use [12]. One aspect that needs consideration is whether CRC is detected during routine screening or upon colonoscopy after suspicious bleeds. Aspirin has been suggested to cause premalignant polyps to bleed, thereby precipitating colonoscopy and polypectomy prior to malignant CRC development [13]. In this scenario, the benefit of aspirin on CRC risk may not be mechanism-based, but instead due to its adverse effects favouring timely detection of the tumor.

The simulated 60–69 year-old cohort were attributed a lower prevalence of traditional CV risk factors than the younger 50–59 year-old group. This is valid from the viewpoint of modelling cohorts with a comparable net baseline risk, since age is per se a strong driver of CV risk, [14] but makes comparison of the age groups difficult. Assuming a higher baseline risk burden in the younger cohort, this will – 10 years on – equate to a higher total CV risk than in the original 60–69 year-old cohort. Moreover, a possible skewing of the risk–benefit profile of aspirin by comorbidites and associted therapies is not accounted for. A further limitation, which the authors critically discuss, is the assumption that baseline characteristics with the exception of age and CV status remain constant during follow-up, which does not take into consideration possible changes in nutritional or lifestyle habits, or other confounders such as onset of non-CV diseases. What the study can also not account for is the response to aspirin on distinct CRC phenotypes – recent evidence suggests that molecular pathological signatures of CRC subtypes determine the risk reduction by aspirin [15]. This is certainly an aspect to consider in follow-up models.

National public-health policies are ideally based on individual-level data for the entire adult population of a nation. This is rarely if ever available. Micro-simulation models such as the one described here [11] that built on high quality parameters, can at least estimate the net health utility in a representative model population, complementing the evidence from RCT and meta-analyses. The decision to prescribe aspirin will, however, remain a personalised one, based on the individual risk profile and preferences of the patient.

Declaration of Competing Interest

References

[1] M. Galli, F. Andreotti, D. D'Amario, R. Vergallo, R.A. Montone, G. Niccoli, F. Crea, Randomised trials and meta-analyses of double vs triple antithrombotic therapy for atrial fibrillation-ACS/PCI: A critical appraisal, Int J Cardiol Heart Vasc. 28 (2020) 100524.

[2] R. Wakili, L. Riesinger, A.C. Fender, D. Dobrev, Double Jeopardy: Will the new trials tell us how to manage patients with atrial fibrillation and coronary artery disease?, Int J Cardiol Heart Vasc 23 (2019) 100369.

[3] D.J. Angiolillo, D. Capodanno, Aspirin for Primary Prevention of Cardiovascular Disease in the 21(st) Century: A Review of the Evidence, Am J Cardiol. 144 (Suppl 1) (2021) S15–s22.

[4] K. Schrör, S.D. Kristensen, R.F. Storey, F.W.A. Verheugt, Aspirin and Primary Prevention in Patients with Diabetes-A Critical Evaluation of Available Randomized Trials and Meta-Analyses, Thromb Haemost. 119 (2019) 1573–1582.

[5] S. Ma, T. Han, C. Sun, C. Cheng, H. Zhang, G. Qu, C. Bhan, H. Yang, Z. Guo, Y. Yan, C. Cao, Z. Ji, Q. Zhou, Does aspirin reduce the incidence, recurrence, and mortality of colorectal cancer? A meta-analysis of randomized clinical trials, Int J Colorectal Dis. 36 (2021) 1653–1666.

[6] M. Suzuki, H. Tomoike, T. Sumiyoshi, Y. Nagatomo, T. Hosoda, M. Nagayama, Y. Ishikawa, T. Sawa, S. Iimuro, T. Yoshikawa, S. Hosoda, Incidence of cancers in patients with atherosclerotic cardiovascular diseases, Int J Cardiol Heart Vasc. 17 (2017) 11–16.

[7] R. Kooiker, H.C. Boshuizen, Internal consistency of a synthetic population construction method for chronic disease micro-simulation models, PLoS One. 13 (2018) e0205225.

[8] T.A. Gaziano, A. Pandya, S. Sy, T.V. Jardim, J.M. Ogden, A. Rodgers, M.C. Weinstein, Modeling the cost effectiveness and budgetary impact of Polypills for secondary prevention of cardiovascular disease in the United States, Am Heart J. 214 (2019) 77–87.

[9] U. Baber, D.E. Leisman, D.J. Cohen, C.M. Gibson, T.D. Henry, G. Dangas, D. Moliterno, A. Kini, M. Krucoff, A. Colombo, A. Chieffo, S. Sartori, B. Witzenbichler, P.G. Steg, S.J. Pocock, R. Mehran, Tailoring Antiplatelet Therapy Intensity to Ischemic and Bleeding Risk, Circ Cardiovasc Qual Outcomes. 12 (2019) e004945.

[10] C. Reynard, N. Morris, P. Moss, H. Jarman, R. Body, Optimising antiplatelet utilisation in the acute care setting: a novel threshold for medical intervention in suspected acute coronary syndromes, Emerg Med J. 36 (2019) 163–170.

[11] al Be. Public health impact of low-dose aspirin on colorectal cancer, cardiovascular disease and safety in the UK – Results from micro-simulation model. IJC Heart Vasculature 36 (2021) 100851.

[12] Y. Zhang, A.T. Chan, J.A. Meyerhardt, E.L. Giovannucci, Timing of Aspirin Use in Colorectal Cancer Chemoprevention: A Prospective Cohort Study, J Natl Cancer Inst. 113 (2021) 841–851.

[13] F.S. Troelsen, D.K. Farkas, R. Erichsen, H.T. Sørensen, Risk of lower gastrointestinal bleeding and colorectal neoplasms following initiation of low-dose aspirin: a Danish population-based cohort study, BMJ Open Gastroenterol. 7 (2020).

[14] M. Sato, Y. Sakata, K. Sato, K. Nochioka, M. Miura, R. Abe, T. Oikawa, S. Kasahara, H. Aoyanagi, S. Yamanaka, T. Fujihashi, H. Hayashi, T. Shiroto, K. Sugimura, J. Takahashi, S. Miyata, H. Shimokawa, Clinical characteristics and prognostic factors in elderly patients with chronic heart failure -A report from the CHART-2 study, Int J Cardiol Heart Vasc. 27 (2020) 100497.

[15] E.L. Amitay, P.R. Carr, L. Jansen, V. Walter, W. Roth, E. Herpel, M. Kloor, H. Bläker, J. Chang-Claude, H. Brenner, M. Hoffmeister, Association of Aspirin and Nonsteroidal Anti-Inflammatory Drugs With Colorectal Cancer Risk by Molecular Subtypes, J Natl Cancer Inst. 111 (2019) 475–483.

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