research

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Haemodynamic management during major surgery

ORIGINAL RESEARCH Randomised clinical trial

Cardiac output guided haemodynamic therapy for patients undergoing major gastrointestinal surgery

OPTIMISE II Trial Group

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Study question Does the use of a haemodynamic intervention comprising cardiac output guided intravenous fluid therapy with low dose inotrope infusion reduce infections and other complications after major elective gastrointestinal surgery?

Methods OPTIMISE II was an international, multicentre, randomised trial conducted in 55 hospitals in the UK (n=14 hospitals), Spain (n=9), Brazil (n=7), Canada (n=5), US (n=5), Germany (n=4), Poland (n=4), Australia (n=3), Switzerland (n=2), Jordan (n=1), and Romania (n=1). Recruitment took place from 26 January 2017 to 13 September 2022. 2498 patients aged 65 years and older with an American Society of Anesthesiologists physical status classification of II or greater and undergoing major elective surgery involving the gastrointestinal tract with an expected duration of more than 90 minutes were eligible. Surgical procedure categories were resection of colon, rectum, or small bowel; resection of pancreas and bowel; resection of stomach (non-obesity surgery); resection of oesophagus (non-obesity surgery); obesity surgery; and other surgery involving gut resection. Participants were randomly assigned to minimally invasive cardiac output guided intravenous fluid therapy with low dose inotrope infusion during and four hours after surgery, or to usual care without cardiac output monitoring. The primary outcome measure was postoperative infection within 30 days of randomisation, defined using US Centers for Disease Control and Prevention criteria as one or more of superficial, deep, or organ space surgical site infection, pneumonia, urinary tract infection, laboratory confirmed bloodstream infection, or infection of uncertain source. The primary outcome was assessed using information from the medical record and from contact with patients. Safety outcomes were acute cardiac events within 24 hours and 30 days. Secondary outcomes were acute kidney injury within 30 days and mortality within 180 days.

Study answer and limitations Postoperative infection within 30 days of randomisation occurred in 289/1247 (23.2%) patients in the intervention group and

283/1247 (22.7%) in the usual care group (adjusted odds ratio 1.03 (95% confidence interval 0.84 to 1.25); P=0.81). Acute cardiac events within 24 hours occurred in 38/1250 (3.0%) patients in the intervention group and 21/1247 (1.7%) in the usual care group (adjusted odds ratio 1.82 (1.06 to 3.13); P=0.03). This difference was primarily due to an increased incidence of arrhythmias among intervention patients. Acute cardiac events within 30 days occurred in 85/1249 (6.8%) patients in the intervention group and 79/1247 (6.3%) in the usual care group (adjusted odds ratio 1.06 (0.77 to 1.47); P=0.71). Other secondary outcomes did not differ. Owing to the nature of the intervention, it was not possible to conceal group allocation from the clinicians; however, masking procedures during data collection and a range of other measures helped reduce bias.

What this study adds This clinical effectiveness trial in patients undergoing major elective gastrointestinal surgery did not provide evidence that cardiac output guided intravenous fluid therapy with low dose inotrope infusion could reduce the incidence of postoperative infections. The intervention was associated with an increased incidence of acute cardiac events within 24 hours, in particular tachyarrhythmias. Based on these findings, the routine use of this treatment approach in unselected patients is not recommended.

Funding, competing interests, and data sharing
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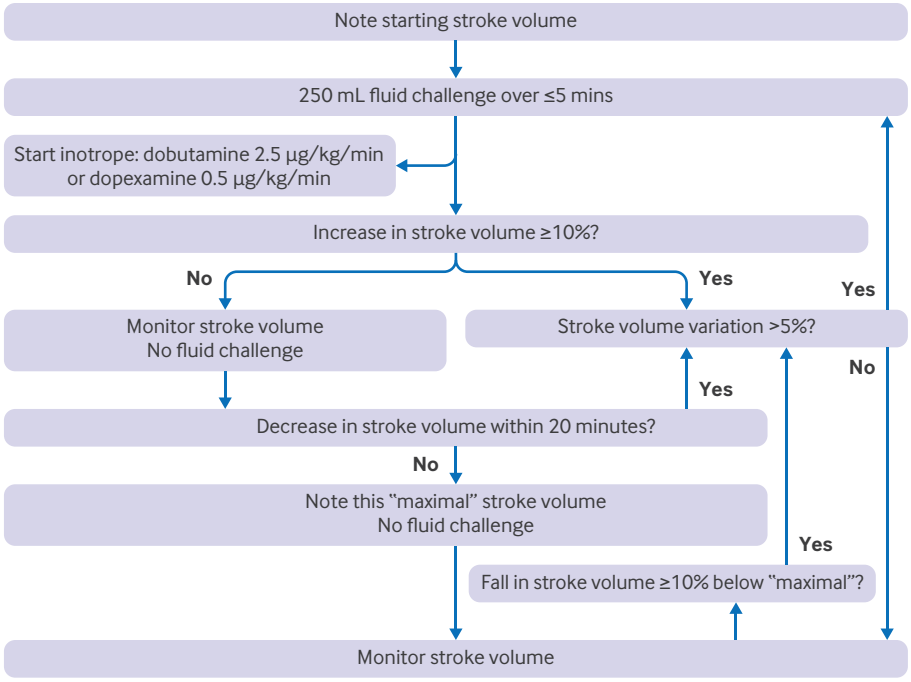
Study registration ISRCTN Registry ISRCTN39653756.



General haemodynamic measures (all patients)
1. Maintenance fluid at 1 mL/kg/h—dextrose 5% recommended
2. Tranfuse blood to maintain haemoglobin >80 g/L
3. Clinician retains discretion to adjust therapy if concerned about risks of hypovolaemia or fluid overload
4. Mean arterial pressure 60-100 mm Hg; SpO_2 ≥94%; temperature 37˚C; heart rate <100 beats/min

Algorithm for cardiac output guided haemodynamic therapy for participants in the intervention group. The listed general haemodynamic measures were applied to all trial participants (intervention and control groups)

Main results for analysis of primary, safety, and secondary outcomes. Values are number (percentage) unless stated otherwise

	Summary measure		Fully adjusted primary analysis model		
	Intervention (n=1251)	Usual care (n=1247)	Adjusted odds ratio (95% CI)	P value	Adjusted difference in percentage points (95% CI)
Postoperative infection <30 days of randomisation (primary outcome)	289 (23.2)	283 (22.7)	1.03 (0.84 to 1.25)	0.81	0.4 (−3.4 to 4.2)
Acute cardiac event <24 hours of randomisation (safety outcome)	38 (3.0)	21 (1.7)	1.82 (1.06 to 3.13)	0.03	1.3 (0.1 to 2.5)
Acute cardiac event <30 days of randomisation (safety outcome)	85 (6.8)	79 (6.3)	1.06 (0.77 to 1.47)	0.71	0.4 (−1.6 to 2.3)
Acute kidney injury <30 days of randomisation	40 (3.2)	32 (2.6)	1.24 (0.77 to 2.00)	0.37	0.6 (−1.1 to 2.3)
Mortality <180 days of randomisation	68 (5.4)	84 (6.7)	0.76 (0.54 to 1.07)	0.12	−1.5 (−3.5 to 0.5)

CI=confidence interval.

More than 300 million major surgeries are performed each year, but perioperative morbidity and mortality remain a problem for high risk surgeries.[1 2]

In 1988, a trial showed for the first time that a protocol involving inotropic infusions and fluid therapy could reduce mortality rates for high risk surgeries.[3] The general concept was to improve oxygen delivery by achieving supranormal cardiac output with fluid loading and inotropic agents to reduce organ dysfunction and mortality.

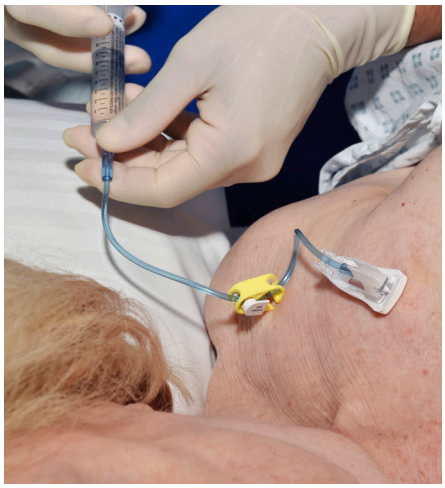
Numerous clinical studies subsequently found that haemodynamic goal directed therapy decreased postoperative morbidity.[4] Despite national and international recommendations, however, monitoring of cardiac output is not well implemented for high risk surgeries owing to its complexity and invasiveness.[5 6] One target could be to use a less invasive, user friendly device at the bedside. The OPTIMISE II Trial Group's study evaluated such a strategy.[7]

OPTIMISE II was a large, multicentre, international randomised clinical trial designed to assess whether minimally invasive cardiac output guided intravenous fluid therapy with low dose inotrope infusion reduced postoperative infection rates after high risk gastrointestinal surgeries compared with usual care without cardiac monitoring.

The trial design overcame several major limitations that have hampered previous studies. The study population was less heterogeneous than in earlier studies, comprising patients with an increased risk of complications undergoing major elective gastrointestinal surgery. The intervention algorithm was clear and easy to use, and it was in use from the start of general anaesthesia until four hours after surgery, allowing an extended period for optimisation of haemodynamic management.

The multicentre design and the inclusion of nearly 2500 patients in 55 hospitals from 11 countries was another strength.

The trial found that haemodynamic therapy including inotropic agents and fluid loading directed by less invasive cardiac output monitors was ineffective in reducing postoperative infections compared with usual care. Secondary outcomes (acute kidney injury within 30 days and mortality within 180 days) and acute cardiac events within 30 days were similar between groups. However, more cardiac events occurred in the first 24 postoperative hours with the cardiac output guided haemodynamic therapy algorithm, especially secondary to the occurrence of cardiac arrhythmia.



P. MARAZZI/SPL

These results could be seen as encouraging because patients in the control group reflected the large improvements in routine perioperative care

What explains the findings?

Several reasons could explain these findings. First, dobutamine has been used as an inotropic drug to improve tissue oxygenation by improving both cardiac output and microcirculation.

Dobutamine has a narrow therapeutic range and its concentration within the therapeutic range can generate cardiovascular arrhythmias.[8] More patients receiving a low dose dobutamine infusion (2.5 µg/kg/min) experienced arrhythmias, showing a negative benefit-risk balance in the intervention group. For this reason, the authors concluded rightly that low dose inotrope infusions in patients undergoing gastrointestinal surgery should be avoided.

Second, surgeries have become shorter and less invasive from the first published goal directed therapy in perioperative setting.[9] Over the past 15 years, technological advancements have transformed many open surgeries into much less invasive laparoscopic or robotic procedures.[9] Moreover, the major development of enhanced recovery after surgery has been described as key to improving the postoperative prognosis of high risk surgical patients, especially in major gastrointestinal surgery.[10 11]

Optimising fluid loading, using light anaesthesia with sedation monitoring and rapid elimination drugs, decreasing drainage use, and promoting early mobilisation are part of routine care and could explain the improved prognosis in the control group in this study compared with previous studies.

Recent improvements in perioperative care, such as maintaining better blood pressure with the use of vasopressors and preventing pulmonary complications using protective ventilation might also have contributed to reducing the expected effect of the protocol.[12 13]

Third, the haemodynamic monitoring measurement, particularly for cardiac output, might have lacked precision. Indeed, the measurement variation of the non-invasive monitor could make it difficult to accurately capture changes in stroke volume,[14 15] and to ascertain the level to which the targeted range of 10% change in stroke volume was met. The combined volumes of fluids given during the overall period were similar between the two study groups. The lack of precision of haemodynamic measurement or the adapted fluid loading in the control group without cardiac output monitoring may explain the absence of benefit for the intervention.

In conclusion, the findings of the OPTIMISE II trial are disappointing because this large and robust trial, long awaited as a major study for perioperative optimisation after many publications with serious limitations, did not find benefit from the cardiac output guided haemodynamic therapy algorithm. However, these results could be seen as encouraging because patients in the control group reflected the large improvements in routine perioperative care for major gastrointestinal surgery.

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Intake of chocolate and risk of type 2 diabetes

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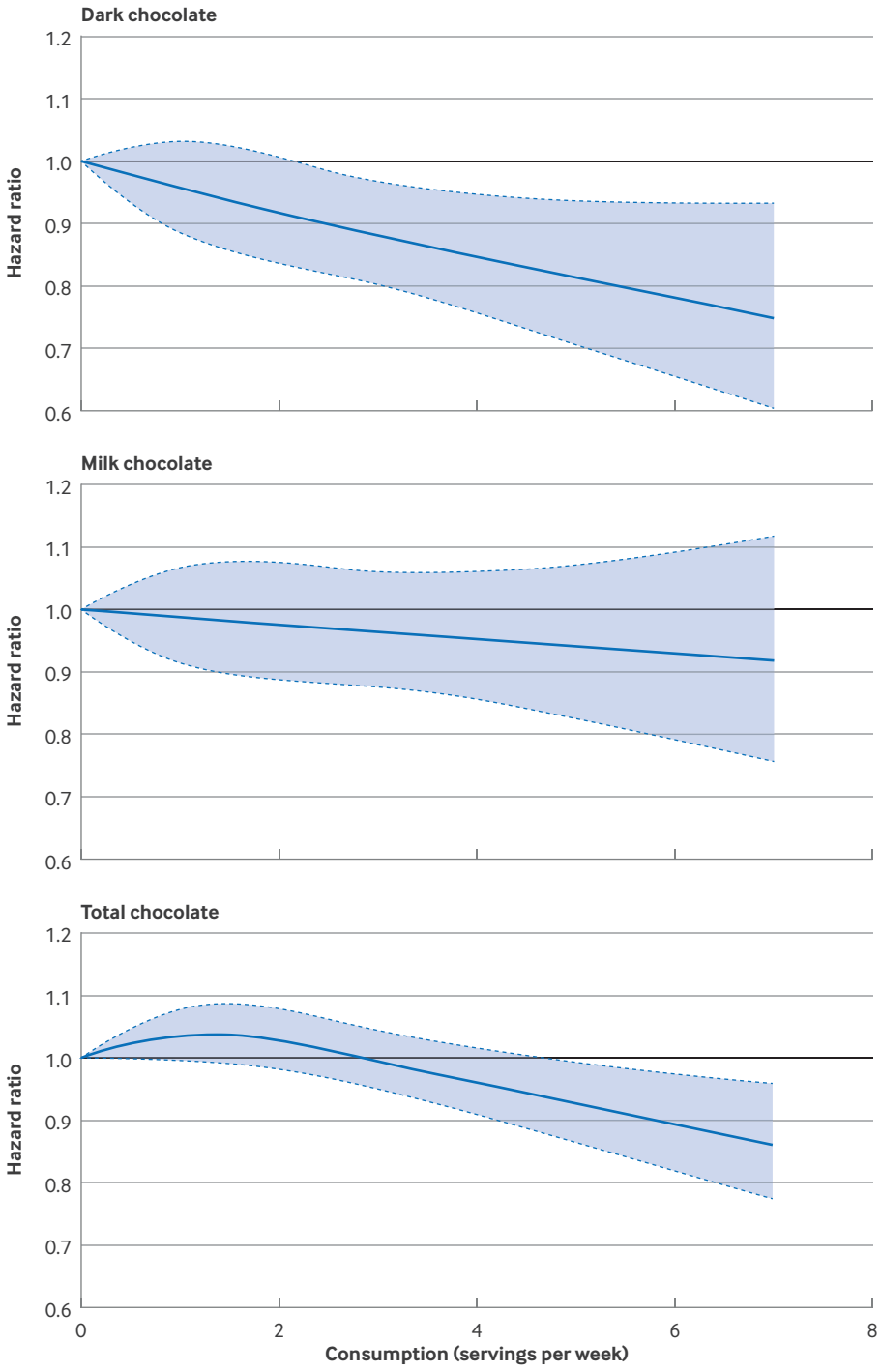
Study question What are the associations between intake of dark, milk, and total chocolate and risk of type 2 diabetes in the US?

Methods This prospective cohort study analysed data from three large US cohorts: the Nurses' Health Study (NHS; 1986-2018), Nurses' Health Study II (NHSII; 1991-2021), and Health Professionals Follow-Up Study (HPFS; 1986-2020). At baseline, a total of 192 208 participants without diabetes, cardiovascular disease, or cancer were included in the analyses of total chocolate intake. 111 654 participants were included for analyses by chocolate subtype, with data on intake collected from 2006 for NHS and HPFS and from 2007 for NHSII. The primary outcome was the incidence of self-reported incident type 2 diabetes, confirmed by a validated supplementary questionnaire. Cox proportional hazards regression was used to estimate hazard ratios and 95% confidence intervals (CIs) for type 2 diabetes according to chocolate consumption.

Study answer and limitations In the primary analyses for total chocolate, 18 862 people with incident type 2 diabetes were identified during 4 829 175 person years of follow-up. After adjusting for personal, lifestyle, and dietary risk factors, participants consuming ≥5 servings/week of any chocolate showed a significant 10% (95% CI 2% to 17%; P trend=0.07) lower rate of type 2 diabetes compared with those who never or rarely consumed chocolate. In analyses by chocolate subtypes, 4771 people with incident type 2 diabetes were identified. Participants who consumed ≥5 servings/week of dark chocolate showed a significant 21% (5% to 34%; P trend=0.006) lower risk of type 2 diabetes. No significant associations were found for milk chocolate intake. Spline regression showed a linear dose-response association between dark chocolate consumption and risk of type 2 diabetes (P for linearity=0.003), with a significant risk reduction of 3% (1% to 5%) observed for each serving/week of dark chocolate consumption. Milk chocolate but not dark chocolate intake was positively associated with weight gain. Limitations included potential residual confounding and limited generalisability to non-white populations or those with different socioeconomic backgrounds.

What this study adds Increased consumption of dark, but not milk, chocolate was associated with lower risk of type 2 diabetes. Increased consumption of milk, but not dark, chocolate was associated with long term weight gain.



Multivariable adjusted, pooled, dose-response associations between chocolate intake and risk of type 2 diabetes in NHS, NHSII, and HPFS. For dark and milk chocolate, follow-up periods were 2006-18 for NHS, 2007-21 for NHSII, and 2006-20 for HPFS. For total chocolate, follow-up periods were 1986-2018 for NHS, 1991-2021 for NHSII, and 1986-2020 for HPFS. NHS=Nurses' Health Study; NHSII=Nurses' Health Study II; HPFS=Health Professionals Follow-up Study

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