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Title: Perioperative thromboprophylaxis is highly variable in general surgery: results from a multicentre survey

Short title: Chemoprophylaxis in general surgery

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/ans.16223](https://doi.org/10.1111/ans.16223)

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Figures: 1. Tables: 1. Appendix: 1

Disclosure statement: The authors have no conflicts of interest to declare

Word count: 1200 including main text, references, tables and figures

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Perspective

General surgical patients who undergo major operations are at risk (0.3-40%) of venous thromboembolism (VTE) (1). This incurs significant morbidity and healthcare costs. Therefore, the Royal Australasian College of Surgeons and healthcare agencies recommend routine thromboprophylaxis in the absence of clear contraindications (2, 3). However, the optimal time to initiate chemoprophylaxis in the perioperative period remains unclear, resulting in variable practices. To understand this heterogeneity, the PROTECTinG (Perioperative Timing of Elective Chemical Thromboprophylaxis in General surgery) investigators, through the VERITAS collaborative, have conducted a multi-centre survey of trainees and surgeons, characterising their preferences for thromboprophylaxis in general surgical patients. This study received multicentre ethics approval (35678).

We designed a 11-point questionnaire asking trainees (n=26), fellows (n=16) and consultants (n=86) from different subspecialties, their decision-making around thromboprophylaxis during elective major surgeries (**Appendix S1**). We defined major surgery as any procedure >45 minutes. Timing of chemoprophylaxis was classified as pre-op, intra-op or post-op when administered before knife-to-skin, during surgery or after skin closure respectively. This study was conducted between 05/08/2019 and 02/02/2020. Surveys were distributed in person across seven Victorian hospitals servicing three (Austin, Northern and Eastern Health) healthcare networks.

Surveys were completed by 26 (100%) trainees, 16 (100%) fellows and 72 (84%) consultants resulting in an overall response rate of 89%. All subspecialties were evenly represented. These included 21 (18%) breast, 22 (19%) endocrine/head/neck, 24 (21%) oesophago-gastric, 19 (17%) hepatobiliary, 23 (20%) colorectal, and 65 (57%) general surgical participants. 41 (36%) respondents had overlapping specialties. Similar representation from each healthcare network (Austin: 27%, Eastern: 33% and Northern: 40%) was also noted. Overall, anti-thrombotic stockings and sequential compression devices were used by 95% and 99% of respondents respectively.

We found significant heterogeneity between consultants, fellows, trainees, healthcare networks and subspecialties with respect to the consistency, type and timing of chemoprophylaxis. Although all respondents used

chemoprophylaxis, only 58% of hepatobiliary specialists do so routinely compared with 87% from the oesophago-gastric group (**Fig 1a**). Whilst enoxaparin was the most commonly used anticoagulant overall, only 63% of respondents from network B prescribed this agent (**Fig 1b**). The remaining 24% and 13% utilised heparin and dalteparin respectively. This is compared to network C, where 96% of respondents preferred enoxaparin.

The greatest variability was seen in the timing of chemoprophylaxis (**Fig 1c**). 44% of fellows commenced chemoprophylaxis post-operatively compared with only 23% of consultants. Additionally, whilst 35% of colorectal specialist utilised chemoprophylaxis pre-operatively, this increased to 74% amongst hepatobiliary surgeons. Moreover, 50% of respondents from network B administer chemoprophylaxis post-operatively, while only 16% do so from network A. Of those who initiate chemoprophylaxis post-operatively, 12%, 69% 16% and 3% apply it immediately after skin closure, 6 hr post-op, 8 pm on the same day, and 8 am the following day, respectively.

The majority of respondents based their practices on personal experience and surgical dogma (**Fig 1d-e**). Only 40% used clinical guidelines to aid initiating chemoprophylaxis. Interestingly, 65% believed there is strong evidence (prospective cohort studies and randomised controlled trials) to guide the timing of chemoprophylaxis in the perioperative period (**Fig 1f**). When asked about factors that may influence clinical practice, most respondents cited the occurrence of 'on-table' VTE, and ensuring timely chemoprophylaxis as the main reasons for its pre-operative usage. In contrast, fear of bleeding and use of spinal anaesthesia were the main drivers for post-operative chemoprophylaxis (**Table 1**).

Our study has highlighted the significant variability in the use and timing of chemoprophylaxis amongst general surgeons, a finding that is shared internationally (4). This has clinical importance given that its inappropriate use may precipitate adverse outcomes. For example, in patients undergoing elective cholecystectomies, early chemoprophylaxis has been associated with increased rates of bleeding compared with its post-operative usage (5). Moreover, findings from the Victorian Audit of Surgical Mortality identified that inappropriate use of thromboprophylaxis repeatedly contributed to surgical mortality (6).

Chemoprophylaxis requires balancing the risk of bleeding with thromboembolic protection. This may explain the practice variation between subspecialties, as different surgeries and patients carry different bleeding and thrombotic risks. However, given that each healthcare network had similar subspecialties, we were somewhat surprised to see such variation between them.

Interestingly, a majority of clinicians believe there is strong evidence to guide chemoprophylaxis timing in general surgery. To our knowledge, the PROTECTinG study is the first to formally address this issue. It is important to recognise that early clinical trials from which current practices are founded (7, 8), did not compare pre-operative versus post-operative chemoprophylaxis. Additionally, the dogma that VTE occurs 'on-table' has never been proven. Furthermore, our finding that many surgeons prescribed chemoprophylaxis to be administered pre-operatively because of concerns regarding the reliability of post-operative administration, highlights an obvious area for quality improvement in our hospitals.

In conclusion, perioperative chemoprophylaxis in general surgery is highly variable. This likely reflects poor evidence, a lack of consensus guidelines, and practice based on dogma and suboptimal institutional factors. **Towards standardising thromboprophylaxis, we need to acknowledge these variances and deficiencies whilst generating the evidence to support change. This will hopefully enable surgical subspecialties to reach an evidence-based consensus on perioperative thromboprophylaxis.**

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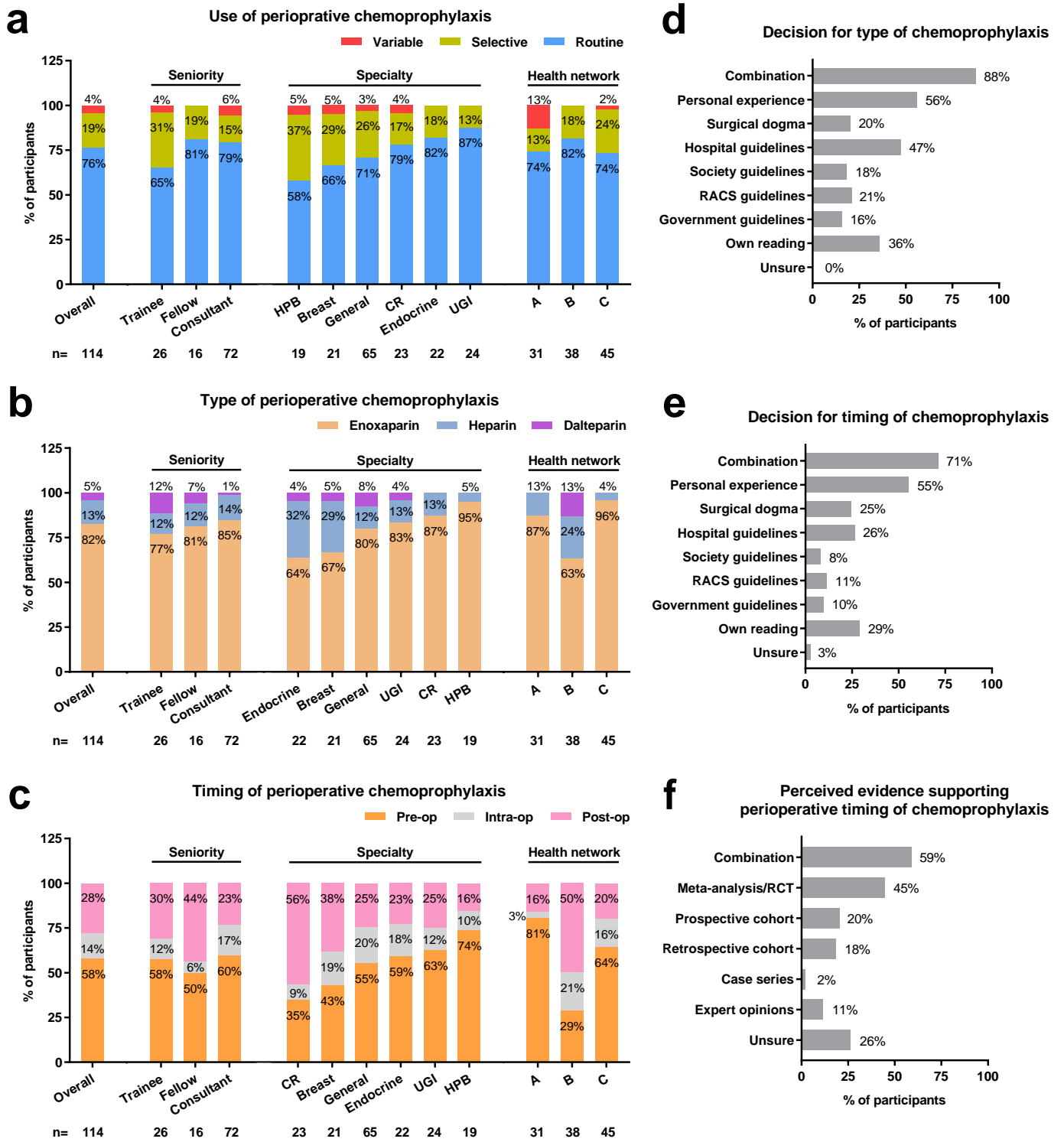
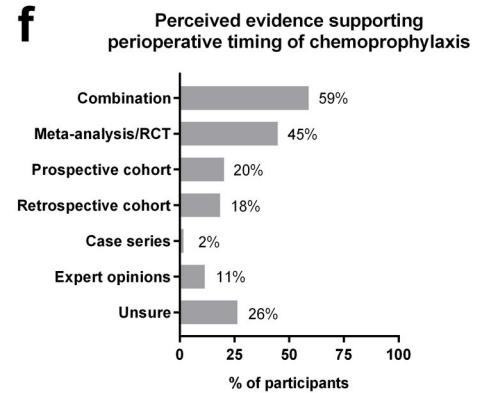
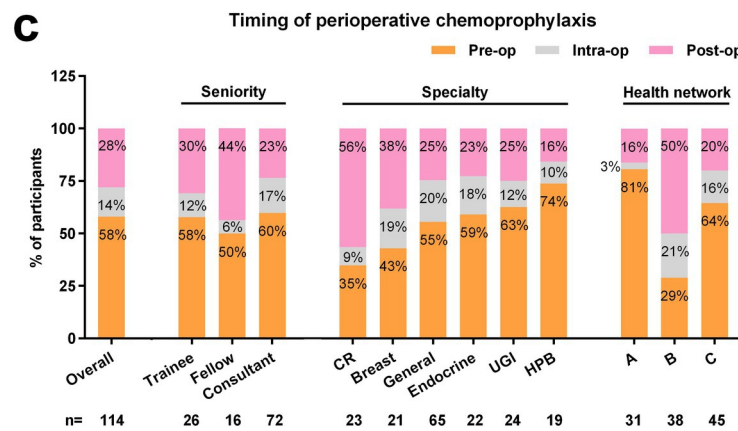
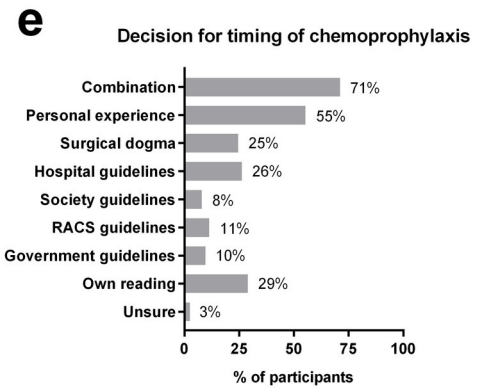
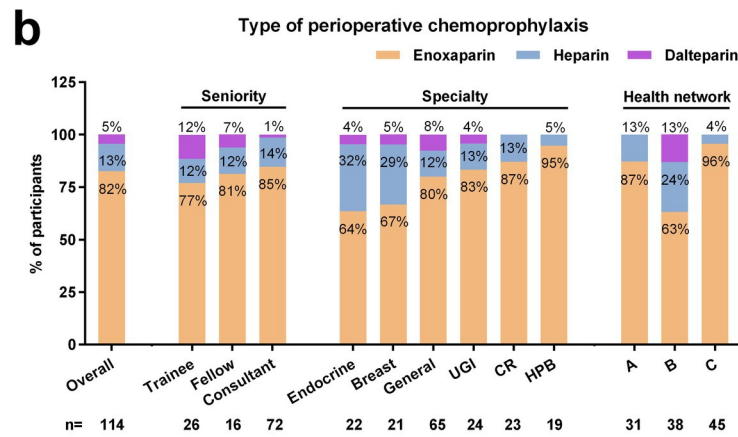
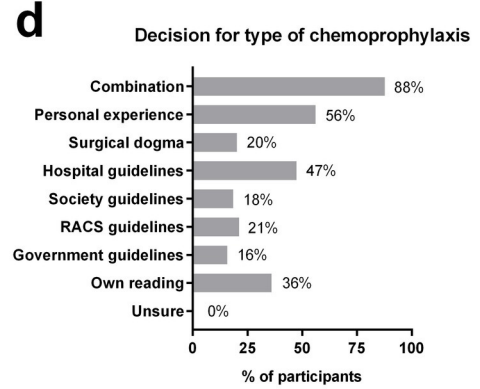
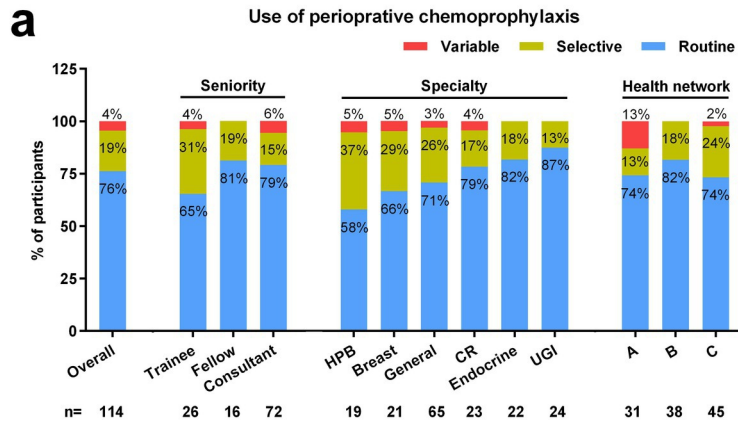


Figure 1. Percentage utilisation (a), type (b) and timing (c) of chemoprophylaxis in the perioperative period. Reasons for type (d) and timing (e) of chemoprophylaxis, and perceived evidence supporting practice (f). CR: colorectal, HPB: Hepatobiliary-pancreas, UGI: Upper gastrointestinal, RACS: Royal Australasian College of Surgeons.

Table 1. Reasons for practice variability

Chemoprophylaxis	Reasons	Respondents* n (%)
Pre-op	Venous thromboembolism occurs on-table	15 (22%)
Pre-op	Ensures timely administration	14 (21%)
Post-op	Risk with spinal anaesthesia	11 (16%)
Post-op	Fear of bleeding	8 (12%)
Selective	Based on individual risk	13 (19%)
Selective	Previous adverse outcomes	3 (4%)
Selective	Following hospital guidelines	2 (3%)
Type	Enoxaparin is more effective than heparin	2 (3%)

*Total of 67 responses were received.



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