PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing the appropriateness of prevention and management of venous thromboembolism in Australia: a cross-sectional study
AUTHORS	Hibbert, Peter; Hannaford, Natalie; Hooper, Tamara; Hindmarsh, Diane; Braithwaite, Jeffrey; Ramanathan, Shanthi; Wickham, Nicholas; Runciman, William

VERSION 1 - REVIEW

REVIEWER	Kate Burbury Peter MacCallum Cancer Centre Melbourne Victoria Australia
REVIEW RETURNED	14-Jul-2015

GENERAL COMMENTS	Review of real-world practice in Australia, assessing appropriate prevention and treatment of venous thromboembolism. This is a retrospective case review of a sampled population within Australia (2009-2010) who underwent hospitalization for surgical or medical reasons to assess whether appropriate TE preventative measures were implemented, according to predefined indicators. TE remains one of the most important preventable cause of peri-hospital-associated morbidity/mortality – and appropriate TE prevention continues to be an important clinical priority. This study – although attempting to measure real-world experience for an important safety initiative - has major limitations in data acquisition and assessment, rendering the implications of this study limited, in terms of generating recommendations or future efforts, to bridge the gap between establishing guidelines and clinical practice. I am unclear exactly what the outcomes of this research are – in particular what they have identified in terms of future recommendations for strategies that will achieve successful and sustainable dissemination and implementation of clinical practice guidelines for appropriate TE preventative measures for real time care in the clinic. There are now robust expert-endorsed, evidence-based guidelines across medical and surgical populations, including subpopulation recommendations. Most clinicians, and indeed many consumers, are very aware of these guidelines and aware of the importance of TE prevention. However translation of these recommendations into the clinic real-time is not yet systematic or routine. This has been clearly demonstrated in many studies, the most notable being ENDORSE. The key issues are, where are the obstacles to sustainable

	implementation – both at an institutional level and subspecialty care groups. I am not convinced that the data presented here provides insight as to where there is an unmet need in terms of implementation of recommendations – see concerns regarding methodology There is no data about the institutions included within the analyses – in particular - whether, at the institutions included in the cohort analysis, there were local institutional guidelines or coordinated guidance and implementation, whether they were aligned with best practice and evidence-based guidelines. Whether there is ease of real-time clinical access to these documents, whether (and how) clinical decision-making is documented As such, I am unclear how this data will contribute to improvement in sustainable implementation of appropriate thromboprophylaxis. I have major concerns regarding methodology to allow this to be contributory to readership and scientific literature 1. Further clarification regarding cohort selection and indicators for appropriate intervention are required – they are referenced in a prior BMJ open access paper from 2012, but simple summary would help readership of this results paper 2. Assessment indicators used for appropriate intervention are not adequate in terms of assessing compliance to guideline recommendations – they are only assessing the presence or absence of intervention. a. Appropriateness of pharmacological (and mechanical) thromboprophylaxis includes regimen, dose, schedule and duration. Using a definer of duration, such as “up to” 35days post major orthopaedic surgery, could mean that patient received 3 days – which is far from compliant. b. Similarly for cancer surgery – implying that administration until discharge or fully mobile is appropriate – is also suboptimal particularly for high-risk major abdomen-pelvic surgery. c. Assessment of mechanical interventions, state the presence of absence, not duration. 3. The sample size, particularly with regards to the varying sub-populations, are really too small to assess whether suboptimal compliance to guideline recommendations. Many of the subgroup encounters were <15. It might have been better to focus on subpopulations within pre-defined hospitals around Australia and assess appropriate intervention across all non-day case surgical procedures, and medical admissions (>defined period). 4. There is no data about the hospitals that were included in the cohort analysis. a. Where they academic/university teaching hospitals, private hospitals etc? b. Number of bed-hospital? c. Where the hospitals assessed for in-house guidance documents, access to documents and local implementation processes? d. Given there were 27 hospitals involved in the cohort analysis, of the sample population in each category, there could have been potentially 1-2 patient per hospital or procedural subgroup. How is this representative of the hospital practice or the subspecialty

	practice? e. Were there clear difference between institutions (rather than random individual patients) with regards to local application and implementation of guidelines – that might provide insights to how to standardize practice and facilitate systematic implementation 5. Patient data is extremely limited – in terms of providing insights to the process a. Was any risk stratification performed b. Were contraindications to thromboprophylaxis assessed – or a barrier to implementation c. Was patient provided with information regarding TE prevention d. Were patients prescribed but did not comply – or just not prescribed e. How was TP documented – did this limit assessment Given the opportunity – both funding and ethics (access) – I hoped more meaningful data that might 1. Provide insight into current clinical practice, guideline access, care coordination 2. Local institutional limitations or barriers to guideline implementation: cost, integration/collaboration, clinical resources, communication, education 3. Consumer perception and education 4. Pragmatic barriers to delivery of appropriate thromboprophylaxis was not ascertained. We are all aware that establishing guidelines does not mean implementation into the clinic – this is particularly apparent in the prevention of TE. We need to understand the barriers to successful (local) guideline development and implementation. There is no data with regards to this, only that in Australia, demonstrated again in this very small subset of patients across a number of institutions, it appears we are still not getting it right. It would be more meanigful to identify where the barriers exist to improve institutional and clinic (doctor and consumer) adherence to the existing, robust evidence-based recommendations that could potentially reduce the rates of TE substantially.

REVIEWER	Jean Yves Le Reste DUMG Brest université de bretagne occidentale France
REVIEW RETURNED	20-Aug-2015

GENERAL COMMENTS	interesting paper, it confirms (for Australia) what has been already shown elsewhere. it is of interest for Australian Physicians to focus on the improvement of their practice. nevertheless the paper needs some improvements: a clear research question should be stated at the end of introduction. This will allow readers to focus on the main results which are of importance and to assess if the method is clear enough to answer that question.

	in method section explain in a clearer way why the development and ratification of indicators were achieved only by haematologists experts. Why no pneumologists or cardiologists were included in the expert panel could be a limit of the study and should be stated somewhere. for discussion : the number of indicators with an insufficient data to report should also be listed in the limits (25 on 44 if my count is correct). the differences between surgical prophylaxis and medical prophylaxis should be highlighted somewhere. In post surgery guidelines are clear. For medicine guidelines are complex and more difficult to implement. In strengths and weaknesses a clearer plan using information, confusion, selection bias and sample's characteristics should be used to enhance the limits of the study. They are numerous but still do not prevent from publishing those interesting results. the following papers could be used in discussion for enhancing the fact that Australia is not the only place where such problem exists and internationalize the results : Can J Cardiol. 2015 Aug 1. pii: S0828-282X(15)00405-5. doi: 10.1016/j.cjca.2015.05.023. [Epub ahead of print] Venous Thromboembolism Prophylaxis on a Cardiology In-Patient Unit: A Surprising Result? Golian M1, Moussa M1, White C2, Aletta G2, Koley L2, Seifer C3. Acta Med Indones. 2015 Apr;47(2):136-45. Underutilization of Anticoagulant for Venous Thromboembolism Prophylaxis in Three Hospitals in Jakarta. Atmakusuma TD1, Tambunan KL, Sukrisman L, Effendi S, Rachman A, Setiawati A, Rinaldi I, Mulansari NA, Rajabto W, Nasution SA, Muhadi, Aninditha T, Sedono R, Sugiarto A, Pitoyo CW, Paramitha D, Astoro NW, Nasution IR. and to enhance the fact that surgery is different from medicine this paper from Australia: Intern Med J. 2015 Mar;45(3):293-9. doi: 10.1111/imj.12675. Thromboprophylaxis in patients undergoing total hip and knee arthroplasty: a review of current practices in an Australian teaching hospital. Pow RE1, Vale PR. Success.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1.

Reviewer 1: Paragraph 1.
”This is a retrospective case review of a sampled population within Australia (2009-2010) who underwent hospitalization for surgical or medical reasons to assess whether appropriate TE preventative measures were implemented, according to predefined indicators.

Reviewer 1: Paragraph 2
TE remains one of the most important preventable cause of peri-hospital-associated morbidity/mortality – and appropriate TE prevention continues to be an important clinical priority."

Our response:
We agree with this summary presented in the first two paragraphs of the reviewer's comments.

Reviewer 1: Paragraph 3
"This study – although attempting to measure real-world experience for an important safety initiative - has major limitations in data acquisition and assessment, rendering the implications of this study limited, in terms of generating recommendations or future efforts, to bridge the gap between establishing guidelines and clinical practice."

Our response:
We recognise, in light of the reviewer's comments, that our paper was misleading in failing to clearly define the aims of our study and analysis. For this we apologise. It was not an attempt 'to measure real-world experience for an important safety initiative', but simply an attempt to provide a baseline estimate of compliance with VTE indicators at a population level as a necessary starting point for tracking progress once intervention strategies have been devised and implemented. Our current research program plans to do this and is essentially framed around "implementation research'. Hence, our paper is not about 'generating recommendations..... to bridge the gap between establishing guidelines and clinical practice'. Had it been, we would agree with all of the reviewer's comments, most of which flow from the understandable misapprehension which arose from our failure to clearly define the aim of our project.

We have therefore altered the introduction and discussion of our abstract to clarify this. The last sentence of the introduction now reads: 'The aim of this paper is to present and discuss the detailed CTA findings for VTE as a baseline for compliance with guidelines at a population level, from which to track progress resulting from future interventions.' The first sentence of our Discussion now reads 'The prevention and management of VTE was appropriate for only half of the at risk patients in our sample; this provides a baseline for tracking progress nationally.' Some words in the abstract have been deleted in order to keep within the word-limit (see track-changes).

Reviewer 1: Paragraph 4
"I am unclear exactly what the outcomes of this research are – in particular what they have identified in terms of future recommendations for strategies that will achieve successful and sustainable dissemination and implementation of clinical practice guidelines for appropriate TE preventative measures for real time care in the clinic."

Our response:
This has been addressed (see above). However in the conclusion, we also propose a way forward: "In line with recommendations arising from the overall CTA study and feedback from clinicians, the challenge is to now move towards agreement on national clinical standards and on the development of indicators and tools to guide, document and monitor the appropriateness of care for VTE. An inclusive, national wiki-based process for achieving this has been proposed.(20) VTE data could then be monitored at hospital level and the data aggregated at national level to track progress and inform policy."

Reviewer 1: Paragraph 5

“There are now robust expert-endorsed, evidence-based guidelines across medical and surgical populations, including subpopulation recommendations. Most clinicians, and indeed many consumers, are very aware of these guidelines and aware of the importance of TE prevention. However translation of these recommendations into the clinic real-time is not yet systematic or routine. This has been clearly demonstrated in many studies, the most notable being ENDORSE.”

Our response:
We agree, and propose steps be taken at the end of the paper. Our surgical results agreed with ENDORSE and our medical results were lower. We had already highlighted these in the Discussion in the third paragraph.

Reviewer 1: Paragraph 6
“The key issues are, where are the obstacles to sustainable implementation – both at an institutional level and subspecialty care groups.”

Our response:
We agree, but this is beyond the scope of this paper, in the light of our comments above.

Reviewer 1: Paragraph 7
“I am not convinced that the data presented here provides insight as to where there is an unmet need in terms of implementation of recommendations – see concerns regarding methodology.”

Our response:
This has been addressed (see above).

Reviewer 1: Paragraph 8
“There is no data about the institutions included within the analyses – in particular - whether, at the institutions included in the cohort analysis, there were local institutional guidelines or coordinated guidance and implementation, whether they were aligned with best practice and evidence-based guidelines. Whether there is ease of real-time clinical access to these documents, whether (and how) clinical decision-making is documented.”

Our response:
Our ethics consent precluded including any individual, institution or facility. The aim was to obtain a national baseline.

Reviewer 1: Paragraph 9
“As such, I am unclear how this data will contribute to improvement in sustainable implementation of appropriate thromboprophylaxis.”

Our response:
See above. Only in so far as the baseline will be provided from which progress can be tracked.

Reviewer 1: Paragraph 10
“I have major concerns regarding methodology to allow this to be contributory to readership and scientific literature.”

Our response:
Again, we believe that the reservations expressed under paragraph 10, subsections 1. and 2. are dealt with in the light of the fact that we were establishing a baseline, and not about evaluating an intervention to improve compliance, nor doing a survey of current practice in Australia at any level of detail. Nevertheless, we have added some detail in the “Development and ratification of indicators”

and the “Recruitment of participants and healthcare providers” sections of the Methods. We resisted going into more detail in many of the CareTrack conditions because of the burden on surveyors, who were already having to review records, determine eligibility and score 522 indicators for 22 conditions.

3. We agree the sample sizes are small, as an inevitable side effect of the population-based approach, but deal with this in the paper under limitations and now suggest extreme caution in interpretation. Again, we were not trying to evaluate any interventions.

4. All the points raised here would be important and relevant to a detailed survey of an intervention, but are beyond the scope of the limited purview of this paper. Ethics consent had been given on the basis that there be no identification, direct or indirect, of any individual, facility or institution.

5. Our comments under paragraph 4 apply to the points raised here. All are highly relevant to the detailed assessment of an intervention, but again are beyond the scope of the limited purview of our paper

The last sentence of the introduction has become: ‘The aim of this paper is to present and discuss the detailed CTA findings for VTE as a baseline for compliance with guidelines at a population level, from which to track progress resulting from future interventions.'

The second sentence under 'Strengths and weaknesses' has become 'However, an unavoidable consequence of this strategy, coupled with finite research funds, is that the numbers of participants and/or eligible encounters are low for some indicators; findings for these must be disregarded or at least interpreted with caution. The review of...'

Response to Reviewer 2.
Reviewer 2: Paragraph 1
“Interesting paper, it confirms (for Australia) what has been already shown elsewhere. it is of interest for Australian Physicians to focus on the improvement of their practice.”

Our response:
We thank the reviewer for supporting the thrust of our paper.

Reviewer 2: Paragraph 2
“Nevertheless the paper needs some improvements: a clear research question should be stated at the end of introduction. This will allow readers to focus on the main results which are of importance and to assess if the method is clear enough to answer that question.”

Our response:
Sentences have been added to the abstract and the end of the introduction to provide a clear research question.

The sentence at the end of the introduction reads:
‘The aim of this paper is to present and discuss the detailed CTA findings for VTE as a baseline for compliance with guidelines at a population level, from which to track progress resulting from future interventions.’

Reviewer 2: Paragraph 3
“In method section explain in a clearer way why the development and ratification of indicators were achieved only by haematologists experts. Why no pneumologists or cardiologists were included in the expert panel could be a limit of the study and should be stated somewhere.”

Our response:
This has been addressed by inserting a sentence at the end of the first sentence under 'Development and ratification of indicators'. 'The opinions of representatives of other specialties were not sought because of logistic constraints.'

Reviewer 2: “For discussion :
the number of indicators with an insufficient data to report should also be listed in the limits (25 on 38 if my count is correct).”

Our response:
This has been done.

Reviewer 2: “The differences between surgical prophylaxis and medical prophylaxis should be highlighted somewhere. In post surgery guidelines are clear. For medicine guidelines are complex and more difficult to implement.”

Our response:
See changes line 3, paragraph 3 in Discussion.

Reviewer 2: “In strengths and weaknesses a clearer plan using information, confusion, selection bias and sample's characteristics should be used to enhance the limits of the study. They are numerous but still do not prevent from publishing those interesting results.”

Our response:
Note that these have been comprehensively addressed in a previous publication: “Runciman WB, Hunt TD, Hannaford NA, Hibbert PD, Westbrook JI, Coiera EW, et al. CareTrack: assessing the appropriateness of health care delivery in Australia. Med J Aust. 2012;197(10):549-50.” We have summarised our findings from this publication in the “Strengths and Weaknesses” section.

Reviewer 2: “The following papers could be used in discussion for enhancing the fact that Australia is not the only place where such problem exists and internationalize the results : “

Our response:
We have inserted into the third paragraph of the 'Discussion' a sentence to address the issue of the indications for medical patients being more complex. It is inserted as the second sentence in paragraph 3. 'Low compliances for medical than surgical patients in the ENDORSE study and the regional hospital are consistent with the more complex indicators for medical patients and have been noted elsewhere (ref three from reviewer 2).

References one and two of reviewer 2 have been inserted in the last sentence of paragraph 2 under the 'Introduction'. This now reads ' However, despite these initiatives and the considerable harm from VTE, much of the care provided for VTE is not in line with CPGs in both the developed (17, add ref 1 from the reviewer 2) and developing worlds (insert ref two from review 2).

VERSION 2 – REVIEW

REVIEWER	Dr Kate Burbury Peter MacCallum Cancer Centre Melbourne, Victoria Australia
REVIEW RETURNED	28-Dec-2015

GENERAL COMMENTS	Comments and suggestions from the prior review have been

	appropriately addressed. The amendments more clearly define the methodology and the authors have applied more appropriate endpoints and objectives. As a consequence, the authors have achieved a better representation of both the data acquired and analysed, as well as the concluding comments.

REVIEWER	Jean Yves Le Reste Department of general practice Research Team SPURBO Faculté de Médecine Université de Bretagne Occidentale 22, av Camille Desmoulins 29238 BREST Cedex 3 FRANCE
REVIEW RETURNED	30-Dec-2015

GENERAL COMMENTS	Important article for pragmatic VTE approach in clinical care. It is now almost fully according with the journal. some minor revision should be undertaken to enhance its quality. In discussion a paragraph should be added to highlight a possible generalization of results. Obviously troubles are the same all over the world as it was described in introduction (ref 18 and 19). The author added en sentence but could go a little further. The limits (strength and weaknesses section) still need some improvement in my point of view and will be clearer if organized through four separate sub sections (samples characteristics, information bias, confusion bias and selection bias). The author could easily handle this with the data they have. Finally the title is not in line with your results. Being more aggressive is possible, for me, as it will be more in line with the article. It would be also more appealing for readers. Something like "Australian VTE, a poor compliance shall push to improvement" could be drafted. So not that much to finalize for success. Well done

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 comment:
Comments and suggestions from the prior review have been appropriately addressed. The amendments more clearly define the methodology and the authors have applied more appropriate endpoints and objectives. As a consequence, the authors have achieved a better representation of both the data acquired and analysed, as well as the concluding comments.
Our response: Thank you for taking the time to review the paper.

Reviewer 2 comment:
In discussion a paragraph should be added to highlight a possible generalization of results. Obviously troubles are the same all over the world as it was described in introduction (ref 18 and 19). The author added en sentence but could go a little further.

Our response: The last line of the abstract has been changed:
“There is a need for national and, ideally, international agreement on clinical standards, indicators and tools to guide, document and monitor care for VTE, and for measures to increase their uptake, particularly where deficiencies have been identified.”
Also, the last line in para 1 on page 19 has been changed:
“This continues to be a problem in both the developed and developing worlds (17-19).”
The second sentence in the Conclusion has been changed, as has the last sentence:
“This is consistent with the lack of a system-wide focus on VTE in Australia as is the case in most of the rest of the world.”
“VTE data could then be monitored at hospital level and the data aggregated at national and, potentially at international levels to track progress and inform policy.”
Reviewer 2 comment:
The limits (strength and weaknesses section) still need some improvement in my point of view and will be clearer if organized through four separate sub section (sample characteristics, information bias, confusion bias and selection bias). The author could easily handle this with the data they have.
Our response: Text has been changed under “Strengths and weaknesses”:
“The key strength of the CTA study is that it is designed to be representative of the Australian population to minimise selection bias, rather than a convenience- or purposive-based sample.”
“The approach used was associated with a high rate of attrition of potential participants and several other sources of possible bias. Although it was not logistically feasible to design sampling so as to eliminate all possible confounders (confusion bias) or have the sample characteristics to exactly match the Australian population, weighting using two methods and five different options made no significant difference to the overall compliance percentage, or that for VTE;(22) this is consistent with providers not altering their clinical practices for patients of different ages, gender, or socio-economic or health literacy status.”