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Routine monitoring for heparin-induced thrombocytopenia following lower limb arthroplasty: Is it necessary? A prospective study in a UK district general hospital

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ABSTRACT

Introduction: Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening condition associated with heparin administration. Many orthopaedic units routinely prescribe low-molecular-weight heparins as thromboprophylaxis after hip and knee arthroplasty.
Hypothesis: We postulated that routine platelet monitoring following heparin administration is of no clinical benefit. We therefore asked: firstly, what was the rate of thrombocytopenia in a large population of patients undergoing lower limb arthroplasty? Secondly, did this rate justify routine platelet monitoring?
Materials and methods: Unless contraindicated, all patients ($n = 1999$, 53.05% female, mean age 69.23 years) at a UK district general hospital undergoing hip and knee arthroplasty were given daily prophylactic enoxaparin. Platelet counts were obtained between the 8th and 10th postoperative days and compared to preoperative baseline. A > 50% fall in platelet count was classified as "possible HIT". The minimal acceptable risk of thrombocytopenia was defined using The American College of Chest Physicians (ACCP) 2012 guidelines, which recommend monitoring platelet counts in patients receiving heparin where the expected risk of HIT is > 1% and by descriptive cost-benefit analysis based on the cost of routine platelet monitoring in the clinical setting.
Results: Complete results were available for 1361 (68.1%) patients, comprising: 653 primary hips, 22 revision hips, 1 hip resurfacing, 665 primary knees, 19 revision knees and 1 unicompartmental knee replacement. Mean platelet level was 281.9 × 109/L preoperatively and 527.83 × 109/L postoperatively. Forty-four patients (3.2%) experienced a postoperative fall in platelet levels. However, no patient experienced a drop in platelets to less than 50% of the preoperative value.
Discussion: The incidence of HIT in the elective arthroplasty population is low. Therefore, routine postoperative monitoring of platelets is not necessary in this population of patients.
Level of evidence: II, prospective study.

1. Introduction

Type II heparin-induced thrombocytopenia (HIT) is a rare but potentially life-threatening immune-mediated reaction to heparin administration characterised by thrombosis. Clinical features of type II HIT include deep venous thrombosis, skin lesions at injection sites, acute systemic reactions, pulmonary embolism, arterial thrombosis (stroke, acute coronary syndrome) and peripheral arterial thrombosis [1–3]. Up to 10% of patients with confirmed HIT require limb amputation and mortality rates range from 10–30% [4–6]. In contrast, type I HIT represents a non-immunological, mild and transient reduction in platelets within a couple of days of heparin exposure, which undergoes a spontaneous recovery and has little long-term clinical significance and is therefore not discussed further.

The cause of HIT has yet to be fully elucidated but the pathophysiology has been widely documented [5]. HIT arises when heparin causes platelet activation and subsequent release of platelet factor

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Table 1
"4 T" Score [19].

Points	2	1	0
Thrombocytopenia	> 50% fall and platelet nadir > 20×10^9/L	30–50% fall or platelet nadir 10–19 $\times 10^9$/L	Fall < 30% or platelet nadir < 10×10^9/L
Timing of platelet count or other clinical sequelae of HIT	Clear onset between days 5 and 10; or ≤ 1 day (if previous heparin exposure within past 30d)	Consistent with immunisation but not clear (e.g. missing platelet counts) or onset of thrombocytopoenia after day 10; or fall ≤ 1d (if heparin exposure 30–100d ago)	Platelet count fall ≤ 4 d (without recent heparin exposure)
Thrombosis or other sequelae (e.g. skin lesions)	New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other cause for thrombocytopoenia not evident	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present

4 (PF4) from platelet alpha-granules. PF4 then complexes with heparin, resulting in a conformational change in the PF4 tetramer. The concentration of heparin required to bring about this conformational shift appears to favour prophylactic, not therapeutic doses [1,7]. Antibodies (which are usually of the IgG subclass) then bind to the PF4/heparin complexes. The IgG-PF4-heparin complex leads to a paradoxical prothrombotic state through several mechanisms including platelet activation, thrombin generation and endothelial injury [8–12].

HIT is usually suspected when there is unexplained thrombocytopenia (as defined by platelet count < 150×10^6/L) in a patient receiving heparin therapy [13]. It is worth noting however, that in 10% of those with HIT, the platelet count fails to fall to below 150×10^9/L [14]: a fall of 30–50% occurs in 90–95% of HIT cases [13–16]. Thrombocytopenia typically begins 5 to 10 days after heparin administration. Exceptions to this rule include rapid-onset HIT (preformed HIT antibodies from a previous episode of heparin exposure are stimulated when the patient is re-challenged by heparin; thrombocytopenia can occur within hours) and delayed-onset HIT (high titres of IgG platelet-activating antibodies are found and the clinical manifestations occur days after heparin cessation) [17].

If a fall in platelet count is detected, further clinical evaluation is required to determine whether HIT is a possibility. The "4 Ts" score evaluates degree of thrombocytopenia, timing of the fall in platelet count, presence of a likely alternative diagnosis and presence of a new or existing but progressive, thrombotic episode (Table 1) [18,19]. Each item is assigned a normalised score to indicate severity where 0 is no clinically significant change, 1 is a moderate change from baseline and 2 is a significant deviation from normal or a significant clinical event. HIT can be excluded on clinical grounds if the 4T score is 0–3 (where the maximum possible score is 8). 4T scores of ≥ 4 warrant further laboratory evaluation with platelet activation assays or immunological assays to prove or exclude a diagnosis of HIT.

If HIT is suspected on clinical grounds (i.e.: 4T score of ≥ 4), anticoagulation with heparin should be stopped immediately until results of confirmatory laboratory results are known. An alternative non-heparin anticoagulant (e.g. direct thrombin inhibitor) at full dose should be commenced whilst confirmatory studies are being performed. If HIT is confirmed, full dose anticoagulation with a vitamin K antagonist should be introduced once the platelet count has returned to the normal range, paying careful attention to measures of haemostasis as definitive anticoagulant therapy is overlapped with the interim agent [18].

Risk of HIT varies between different patient populations for reasons yet to be fully understood. Studies have demonstrated that risks of HIT are higher with prolonged heparin exposure (greater than 4 days); with unfractionated heparin (UFH); in surgical patients; and in female patients [1,4]. It has been proposed that variability in heparin preparations, patient demographics and diagnostic assays may also contribute to the variability in risk [20]. Quantifications of the risk of HIT in orthopaedic patients receiving LMWH vary with estimates ranging from 0.15–0.9% [2,4,20–22].

The American College of Chest Physicians (ACCP) 2012 guidelines recommend monitoring platelet counts in patients receiving heparin where the expected risk of HIT is > 1%. This 2c-grade recommendation suggests that platelet counts are checked between day 4 and 14 or until the heparin is stopped (whichever is sooner) [23]. Routine platelet monitoring for HIT following elective arthroplasty surgery has obvious resource and cost implications and necessitates blood investigations which are unpleasant and inconvenient for patients. Given the variability in estimates of the risk of HIT in elective orthopaedic patients the value of routine monitoring remains unclear and some units therefore still employ routine platelet count monitoring in this patient group.

Martel et al. attempted to quantify the risk of HIT through a meta-analysis and included several papers incorporating orthopaedic patient groups however none addressed the issue of HIT rates in thromboprophylaxis [24]. It is also worth noting that this paper was published prior to the adoption of extended thromboprophylaxis in elective lower limb arthroplasty patients. The authors therefore identified the need for studies to clarify the incidence of HIT in orthopaedic patients receiving thromboprophylaxis. In 2013, a retrospective study by Craik and Cobb attempted to do just this and estimated the incidence of HIT-related thrombosis in patients who had undergone either primary hip or knee arthroplasty as 0.03% [21]. This represented one patient in a cohort of 3515. However, the one patient in the study with thrombocytopenia and associated thrombosis following LMWH administration did not have the recommended HIT confirmatory laboratory studies and was not treated for HIT. It is not therefore possible to conclude that HIT explained the clinicopathologic features in this case.

Therefore, we hypothesised that routine platelet monitoring following heparin administration is not useful in the elective lower limb arthroplasty population at a threshold of > 1% risk of thrombocytopenia, as per ACCP guidelines. In this prospective study, we intended to assess the rate of thrombocytopenia in a large population of patients undergoing lower limb joint reconstruction and whether this observed rate would justify routine platelet monitoring.

2. Materials and methods

In accordance with United Kingdom national guidance, all patients undergoing total knee and hip arthroplasty over a four-year period in a United Kingdom district general hospital were given daily subcutaneous enoxaparin (LMWH) injections, unless contraindicated, until postop days 14 and 28, respectively [25]. Platelet counts were obtained preoperatively to establish baseline levels. Further platelet counts were obtained between the 8th and 10th postoperative days. Had the patient been discharged from hospital at this point this was arranged via community services.

The platelet levels were reported via the pathology results system and recorded in a confidential departmental database. Results were monitored in real time by the elective orthopaedic ward staff.

In total, 1999 patients were eligible for inclusion and complete results were available for 1359 (67.98%) patients. Of these 53.05% were female and the average age of the cohort was 69.23 years. The 1359 patients comprised 653 (48.05%) primary hips, 22 (1.62%) revision hips, 1 (0.07%) hip resurfacing, 665 (48.93%) primary knees, 19 (1.40%) revision knees and 1 (0.07%) unicompartmental knee replacement. Our primary assessment criterion was defined as patients experiencing a fall in platelets of > 50% from the preoperative baseline, which was classified as "possible HIT". We utilised the 4T scoring system as a secondary assessment criterion. A patient experiencing a > 50% fall in platelets from baseline or a 4T score of ≥ 4 warranted further clinical evaluation and confirmatory laboratory studies. Arrangements were in place to contact such patients for further face-to-face clinical/laboratory evaluation.

3. Results

Mean preoperative platelet level was 281.96×10^9/L (SD 76/67; range 65–855 $\times 10^9$/L) and 527.83×10^9/L on postoperative day 1 (160.85; 131–1173 $\times 10^9$/L). The mean percentage platelet change was therefore +93.33% (57.81; −42.71 to +401.28%) (Fig. 1).

Forty-four patients (3.2%) experienced a postoperative drop in platelet levels ranging from a −0.47% to a −42.7% reduction. Two patients had a postoperative platelet count of below 150×10^9/L: 136×10^9/L and 131×10^9/L. No patient experienced a drop in platelet levels to less than 50% of baseline.

Therefore, formal 4T scoring and further confirmatory laboratory studies were not deemed necessary in any patient in the cohort.

4. Discussion

Our results suggest that thrombocytopenia and thrombosis following administration of LMWH for elective arthroplasty patients is an extremely rare event, far below the threshold of 1% justifying platelet count monitoring. The clear majority (96.8%) of patients experienced an increase in platelet numbers postoperatively. A very small minority (3.2%) of patients experienced a postoperative decline in platelet count. However, this postoperative platelet level did not drop to 50% of preoperative levels in any patient. Furthermore, the lowest postoperative platelet count in any patient in the cohort (131×10^9/L) was still well above the typical 'nadir' seen in HIT. These were both considerably higher than the widely reported nadir associated with symptomatic HIT (55×10^9/L) [6,18,21].

Our finding that relatively few patients (3.2% in our investigation) experience a fall in postoperative platelet counts is corroborated in the study of HIT in elective arthroplasty patients by Craik and Cobb in 2013 [21]. They found that only 13 of the 3515 (0.37%) patients investigated experienced relative thrombocytopenia resulting from LMWH administration following elective lower limb arthroplasty. Furthermore, only 1 of the 3515 (0.0284%) patients followed in their study went on to develop thrombosis and it was unclear whether this was related to HIT or not.

Our evidence is contrary to the view Warkentin et al. proposed two decades ago that HIT is a "relatively common" adverse effect of heparin prophylaxis [2]. However, this difference may be explained by the fact that our study and that of Craik and Cobb defined HIT as a > 50% decrease in platelet level whereas Warkentin et al. used the absolute definition of thrombocytopenia (platelet count < 150×10^9/L) as inclusion criteria [2,21]. It is thought that the definition used in this study – rather than using an absolute cut-off value – results in greater diagnostic specificity [1].

We have identified that, although a small minority of elective arthroplasty patients (3.2%) experienced a postoperative drop in platelets, none went on to experience a thrombocytopenia significant enough to prompt further investigation for HIT. This low incidence confirms preexisting evidence in the literature [21]. As such, the observed risk of HIT was considerably lower than the 1% threshold proposed by the ACCP to justify regular platelet surveillance. Hence, regular monitoring of platelets for HIT in elective arthroplasty patients is not only impractical but also unjustifiable given the very low potential to detect HIT. Additionally, the cost for a full blood count in the United Kingdom is estimated at £6 per test [26]. Given the numbers of patients

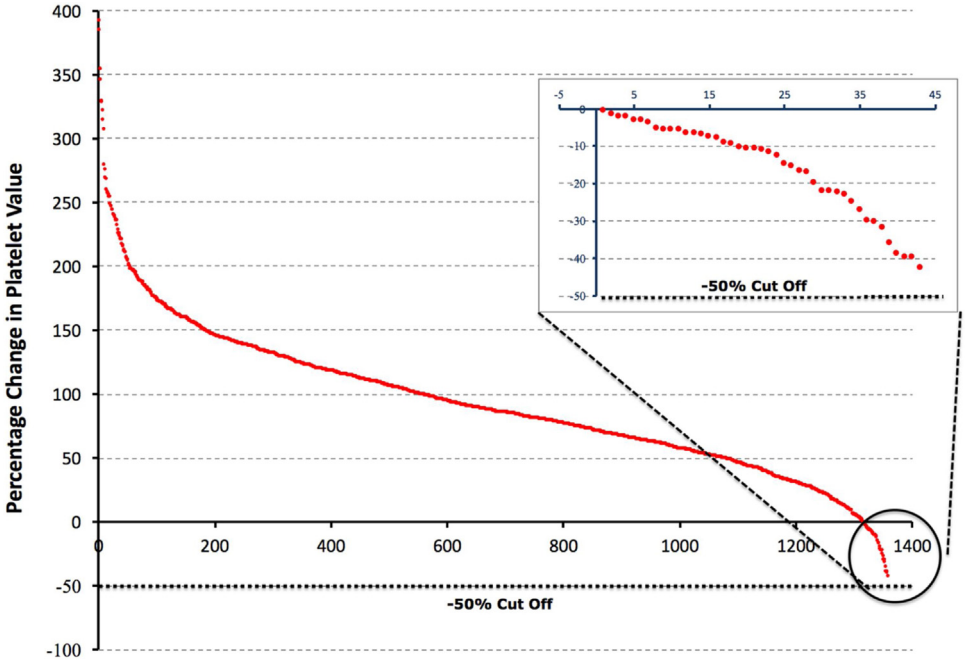

Fig. 1. Relative change in platelet level (postop vs. preop) for each patient in the cohort.

undergoing elective arthroplasty surgery, there is potential for considerable cost saving by avoiding unnecessary platelet monitoring.

Limitations: there were several limitations to our investigation. Firstly, it may be argued that our results are only relevant to patients given enoxaparin as postoperative thromboprophylaxis. However, the higher frequency of HIT in orthopaedic patients is thought to be due to factors other than the dose and type of LMWH. Factors considered of more importance include the duration of exposure to heparin, however, other factors are yet to be fully elucidated. Therefore, our results may still apply to other LMWHs [6,21]. Our definition of "possible HIT" was a postoperative platelet count less than 50% of the preoperative baseline (relative thrombocytopenia). Using this definition for screening, cases of absolute thrombocytopenia (platelet count $< 150 \times 10^9$/L) could theoretically be missed, particularly if patients had a relatively low platelet count preoperatively. However, in our cohort only 2 patients had postoperative platelet levels below 150×10^9/L (136 and 131×10^9/L). Their preoperative platelet levels were 65 and 170×10^9/L respectively; meaning relative changes of +71% and −39%. In 10% of HIT cases, the platelet count does not fall below 150×10^9/L. Hence, measuring relative thrombocytopenia provides greater diagnostic specificity [3].

Identifying HIT via platelet count monitoring following discharge from hospital is inherently impractical due to difficulties in follow-up, particularly if patients have blood tests in the community. Anecdotally, patients report that they experience discomfort and inconvenience for very little perceived gain. Our 67.98% follow-up rate reflects this. Our unit is also hindered by the fact that its catchment area covers a large, mostly rural, geographical area.

Samples were only collected on postoperative day 1 and between days 8 and 10 with the aim of identifying cases of "typical-onset" HIT (this is the most common time frame for HIT to present) [2,4]. Rare presentations of HIT may have been missed from our analysis as a consequence of the sampling method. These may include: rapid-onset HIT, which is usually due to exposure to LMWH in the 3 months prior to postoperative thromboprophylaxis. HIT occurs in these cases 10–12 hours post-heparin administration and always before postoperative day 4 [1,4]. Also, delayed-onset HIT (3–5% of cases) occurs on average at day 14 with a range between – or after – postoperative days 10 and 15. This syndrome always presents after the cessation of LMWH administration [1,4,6].

5. Conclusion

HIT is a rare adverse reaction to heparin administration with the potential to cause significant morbidity and comes with a high-risk of mortality. Administration of LMWHs for VTE prophylaxis in elective lower limb arthroplasty patients is widespread however, regular monitoring for relative and absolute thrombocytopenia is not recommended. We have confirmed that the incidence of HIT in the elective arthroplasty population is extremely low and therefore, routine postoperative monitoring of platelet levels for HIT is not necessary.

Disclosure of interest

The authors declare that they have no competing interest.

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Author contributions

B. Haughton: conception and design of study, acquisition of data, analysis and interpretation of data, drafting, review and revision of the article, final approval of the version to be submitted.

J. Haughton: analysis and interpretation of data, drafting, review and revision of the article, final approval of the version to be submitted.

J.G. Norman: analysis and interpretation of data, drafting, review and revision of the article, final approval of the version to be submitted.

A. Navid, K. Allport: acquisition of data, review of the article, final approval of the version to be submitted.

M. Andrews: conception and design of study, review of the article, final approval of the version to be submitted.

K. Mannan, J. Livesey: conception and design of study, analysis and interpretation of data, review and revision of the article, final approval of the version to be submitted.

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References

[1] DiGiovanni CW. Current concepts review: heparin-induced thrombocytopenia. Foot Ankle Int 2008;29:1158–67.
[2] Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Eng J Med 1995;18:1330–5.
[3] Warkentin TE. Heparin-induced thrombocytopenia. Curr Haematol Rep 2002;1:63–72.
[4] LaMuraglia GM, Houbballah R, Laposata M. The identification and management of heparin-induced thrombocytopenia in the vascular patient. J Vasc Surg 2012;55:562–70.
[5] Linkins L, Bates SM, Lee AYY, Heddle NM, Wang G, Warkentin TE. Combination of 4Ts score and PF4/H-PaGIA for diagnosis and management of heparin-induced thrombocytopenia: prospective cohort study. Blood 2015;126:597–603.
[6] Salter BS, Weiner MM, Trinh MA, Heller J, Evans AS, Adams DH, et al. Heparin-induced thrombocytopenia: a comprehensive clinical review. J Am Coll Cardiol 2016;31:2519–32.
[7] Hassell K. Heparin-induced thrombocytopenia: diagnosis and management. Thromb Res 2008;123:S16–21.
[8] Newman PM, Chong BH. Heparin-induced thrombocytopenia: new evidence for the dynamic binding of purified anti-PF4-hepatin antibodies to platelets and the resultant platelet activation. Blood 2000;96:182–7.
[9] Warkentin TE, Hayward CP, Boshkov LK, Santos AV, Sheppard JA, Bode AP, et al. Sera from patients with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocytopenia. Blood 1994;84:3691–9.
[10] Warkentin TE, Sheppard J-AI. Generation of platelet-derived microparticles and procoagulant activity by heparin-induced thrombocytopenia IgG/serum and other IgG platelet agonists: a comparison with standard platelet agonists. Platelets 1999;10:319–26.
[11] Visentin GP, Ford SE, Scott JP, Aster RH. Antibodies from patients with heparin-induced thrombocytopenia/thrombosis are specific for platelet factor 4 complexed with heparin or bound to endothelial cells. J Clin Invest 1994;93:81–8.
[12] Greinacher A, Pötzsch B, Amiral J, Dummel V, Eichner A, Mueller-Eckhardt C. Heparin-associated thrombocytopenia: isolation of the antibody and characterization of a multimolecular PF4-heparin complex as the major antigen. Thromb Haemost 1994;71:247–51.
[13] Warkentin TE, Roberts RS, Hirsh J, Kelton JG. An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopaedic patients. Arch Intern Med 2003;163:2518–24.
[14] Warkentin TE. Clinical picture of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, editors. Heparin-induced thrombocytopenia. 2nd ed. New York, NY: Marcel Dekker Inc; 2001. p. 43–86.
[15] Greinacher A, Ferner B, Kroll H, Kohlmann T, Warkentin TE, Eichler P. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. Thromb Haemost 2005;94:132–5.
[16] Pouplard C, May MA, Iochmann S, Amiral J, Vissac AM, Marchand M, et al. Antibodies to platelet factor 4-heparin after cardiopulmonary bypass in patients

anticoagulated with unfractionated heparin or a low-molecular-weight heparin: clinical implications for heparin-induced thrombocytopenia. Circulation 1999;9:2530–6.
[17] Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. Ann Intern Med 2001;135:502–6.
[18] Watson H, Davidson S, Keeling D. Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. Br J Haematol 2012;159:528–40.
[19] Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 2006;4:759–65.
[20] Warkentin TE, Sheppard JA, Horsewood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk of heparin-induced thrombocytopenia. Blood 2000;96:1703–8.
[21] Craik JD, Cobb AG. Heparin-induced thrombocytopenia following hip and knee arthroplasty. Br J Haematol 2013;161:255–61.
[22] Warkentin TE, Cook RJ, Marder VJ, Sheppard JA, Moore JC, Eriksson BI, et al. Anti-platelet factor 4/heparin antibodies in orthopedic surgery patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin. Blood 2005;106:3791–6.
[23] Linkins L, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, et al. Treatment and prevention of heparin-induced thrombocytopenia. Antithrombotic therapy and prevention of thrombosis, 9th Ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:e495S–530S.
[24] Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated heparin and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005;106:2710–5.
[25] National Institute for Health and Care Excellence. Venous thromboembolism: reducing the risk. NICE Guideline (CG92); 2015.
[26] Czoski-Murray C, Lloyd Jones M, McCabe C, Claxton K, Oluboyede Y, Roberts J, et al. What is the value of routinely testing full blood count, electrolytes and urea, and pulmonary function tests before elective surgery in patients with no apparent clinical indication and in subgroups of patients with common comorbidities: a systematic review of the clinical and cost-effective literature. Health Technol Assess 2012;16:1–159.