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CLINICAL AND SAFETY OUTCOMES ASSOCIATED WITH TREATMENT OF ACUTE VENOUS THROMBOEMBOLISM: [11-1]

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I hope you will find *Practical Pointers* interesting and helpful.

Richard T. James Jr. M.D.

Editor/Publisher.

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11-1 CLINICAL AND SAFETY OUTCOMES ASSOCIATED WITH TREATMENT OF ACUTE VENOUS THROMBOEMBOLISM: Systematic Review and Meta-Analysis

Venous thromboembolism (VTE), manifested as deep vein thrombosis or pulmonary embolism, is common and is the third leading cause of cardiovascular death. Untreated, acute VTE is associated with mortality up to 25%.

Anticoagulant therapy is effective treatment and prevents recurrent events and death.

Parenteral anticoagulants (unfractionated heparin, low molecular weight heparin, or fondaparinux) with transition to a vitamin K antagonist is the traditional treatment. Parenteral anticoagulation is continued for a minimum of 5 days until the international normalized ratio is 2.0 or higher for at least 24 hours.

The traditional approach to VTE is cumbersome, given that initial therapy must be administered parenterally and the use of a vitamin K antagonist requires frequent laboratory monitoring as well as food and drug restrictions due to adverse interactions.

Oral anticoagulants: direct factor Xa inhibitors—rivaroxaban, apixaban, and endoxaban and direct thrombin inhibitor—dabigatran may offer attractive treatment of VTE.

This article summarizes and compares clinical outcomes and safety associated with various management options for anticoagulation.

METHODS

Low molecular weight heparin
UFH Unfractionated heparin
VKA Vitamin K antagonist
VTE Venous thromboembolism
DVT Deep vein thrombosis embolism
PE Pulmonary LMWH

A systematic search of the literature (1946-2014) found 45 trials (n = 45 000) meeting inclusion criteria. All studies enrolled patients with objectively confirmed VTE or PE.

Outcome measures: Primary outcomes were recurrent VTE or major bleeding.

Major bleeding was defined as at least 1 of: 1) decrease in hemoglobin of at least 2 grams, 2) transfusion of 2 or more units of packed red cells, 3) intracranial or retroperitoneal bleeding or body cavity bleeding, 4) death.

RESULTS

Thirty four trials compared various anticoagulants with LMWH-VKA

Only 1 or 2 trials compared LMWH –dabigatran, LMWH-endoxaban, rivaroxaban alone, and apixaban alone with LMWH-VKA.

Most trials compared UFH-VKA with LMWH-VKA

Median sample size was 298; median follow-up was 3 months.

All trials evaluated patients with DVT, PE or both.

In comparison with the LMWH-VKA combination, all treatment strategies except the UFH-VKA were associated with a lower rate of recurrent VTE events. However, none reached statistical significance.

The UFH-VKA combination had the highest rate of recurrences of VTE compared with LMWH-VKA. (Hazard ratio 1.4)

All remaining treatment strategies did not reveal significant differences in rates of recurrent VTE.

Major bleeding events:

Compared with LMWH-VKA, rivaroxaban alone and apixaban alone were associated with lower bleeding risk (hazard ratios 0.55 and 0.31). All other combinations were associated with bleeding risks that did not differ significantly from LMWH-VKA.

Fatal events from recurrent VTA and from bleeding were rare

DISCUSSION

To date, this is the largest review (45 000 subjects) assessing the outcomes and safety associated with different anticoagulants for treatment of VTE.

All management options, with exception of UFH-VKA, were associated with outcomes similar to the LMWH-VKA combination. UFH-VKA was associated with the highest risk of recurrent VTE.

Apixaban and rivaroxaban without preceding parenteral anticoagulation were associated with reduction in risk of major bleeding compared with LMWH-VKA.

Rivaroxaban, dabigatran, and apixaban are approved for DVT and PE.

LMWH was given along with edoxaban and dabigatran in the first 5 days. Apixaban and rivaroxaban were evaluated without initial use of LMWH. Treatment options using direct oral anticoagulants are associated with similar clinical outcomes as the more traditional strategies using LMWH-VKA.

Direct oral anticoagulants (rivaroxaban and apixaban) seem to be associated with lower risk of major bleeding. Apixaban is also associated with significantly less bleeding compared with LMWH-dabigatran and LMWH-edoxaban.

None of the trial concerned secondary prevention of VTE.

No trials compared the different direct oral anticoagulants with each other.

The costs of the different treatments were not considered.

CONCLUSION

There were no statistically significant differences in clinical and safety outcomes associated with most treatment strategies compared with LWMH-VKA.

However, findings suggest that UFH-VKA is associated with the least effective strategy.

Rivaroxaban alone and apixaban alone may be associated with the lowest risk of bleeding.

JAMA September 12, 2014; 1122-34 First author Lana A Castellucci, University of Ottawa, Canada.

Fundaparinux (*Arixtra*; GlaxcoSmithKline) is chemically related to low molecular weight heparin. It is a factor Xa inhibitor. Unlike direct factor Xa inhibitors, it acts indirectly through antithrombin III. It does not inhibit thrombin. It is given subcutaneously daily. One advantage over the heparins is that the risk of heparin-induced thrombocytopenia is substantially lower. Its renal excretion precludes use in patients with renal dysfunction.

Riveroxaban (*Xarelto*; BAYER, Janssen) a highly selective direct factor Xa inhibitor given orally once a day. It is approved for prophylaxis of deep vein thrombosis after knee and hip replacement surgery, and for prevention of stroke in patients with atrial fibrillation. It has been widely advertized.

Apixaban (*Eliquis*; Pfizer) a direct factor Xa inhibitor approved for treatment and prophylaxis of DVT and PE. It is used for lowering risk of stroke in patients with non-valvular atrial fibrillation, for prevention of DVT following hip and knee replacement surgery. It is given orally once a day. It has been widely advertized.

Edoxaban (*Lixiana*; Daiichi Sankyo) approved for prevention of stroke. Results are similar to other new factor Xa inhibitors.

Factor Xa (activated factor X) is the target of many anticoagulants: UFH, LMWH, fondaparinux, rivaroxaban, apixaban, and edoxaban. It converts prothrombin into thrombin.

Dabigatran (Pradaxa; Boehringer Ingellheim) differs. It is a direct thrombin inhibitor, despite its xa suffix. It is combined with 5-days of initial LMWH.

It is used to prevent stroke in patients with atrial fibrillation, and to prevent DVT and PE.

Capsules contain tartaric acid to facilitate absorption. The low pH may be associated with dyspepsia.

Sourfe: Wikipedia

I welcomed this review of the latest on the new anticoagulants. I believe the direct oral anticoagulants are an important advance in primary care medicine.

The reviews are more detailed than I have indicated.

There is much more to learn. Xarelto and Eliquis are costly—my pharmacy quotes about $400 for a 30 day supply.

11-2 COMPARATIVE EFFECTIVENESS OF PHARMACOLOGIC TREATMENTS TO PREVENT FRACTURES: Update and Systematic Review

Risk factors for osteoporotic fractures include, but are not limited to: increasing age, female sex, post-menopause for women, low body weight, parental history of hip fracture, cigarette smoking, race, hypogonadism, certain medical conditions (particularly rheumatoid arthritis), and certain medications for chronic diseases (e.g. glucocorticoids).

During expected remaining life, 1 in 2 postmenopausal women and 1 in 5 older men are at risk for osteoporotic fractures.

In the past 7 years, several new drugs have been approved for prevention of fractures in men and women with osteoporosis.

Issues about drug treatment for osteoporosis include duration of therapy, safety of long-term treatment, and the role of measurement of bone mineral density (BMD) for screening and for monitoring treatment.

METHODS:

This updated review focuses on comparative benefits and risks of short- and long-term pharmacologic treatment for low bone density (LBD) and issues regarding monitoring and duration of treatment.

The authors conducted a wide-spread search of literature 2005-14. It includes newly approved drugs and adverse effects.

Eligible studies (English language only) were systematic reviews and randomized controlled trials (RCTs) of FDA-approved drugs for men and women with osteoporosis that was not due to a secondary cause (e.g. glucocorticoids and androgen-depredation therapy).

Also included observational studies with more than 1000 participants for adverse events.

The assessments of efficacy and effectiveness used reductions in fracture (all bone sites) as outcomes.

RESULTS

Over 55 000 articles were screened; 315 met eligibility criteria for inclusion.

Fracture prevention:

There is strong evidence that bisphosphonates (alendronate, etidronate, ibandronate, risedronate, zoledronic acid[a]), denosuma[b], teriparatide[c], and raloxifine[d] prevent fractures in women with osteoporosis. The number needed to treat for 1 to 3 years to prevent one fracture varies from 50 to 89.

The principal new efficacy findings:

Zoledronic acid is a bisphosphonate given intravenously: Six placebo-controlled studies of varying doses in over 9000 post-menopausal women showed statistical significant reductions in nearly all types of fractures assessed. Relative risk reductions ranged from 0.23 to 0.73 at 24 to 36 months after initiation of treatment.

Denosumab: Two placebo-controlled trials of over 1000 postmenopausal women followed for 36 months showed significant reductions in each anatomical fracture type (hip, vertebral, non-vertebral and new clinical vertebral). Hazard ratios ranged from 0.31 to 0.80. High strength evidence shows that bisphosphonates, denosumab and teriparatide reduce fractures compared with placebo in postmenopausal women. This translates into a number needed to treat of 60 to 89 to prevent one vertebral fracture and 50 to 67 to prevent one hip fracture over 1 to 3 years.

For men with osteoporosis, there is only one RCT. Nearly 1200 men were randomly assigned to intravenous zolindronic acid vs placebo for 2 years. Approximately 1.05 of actively treated men had clinical fractures vs 1.8% of those receiving placebo. (Hazard ratio = 0.6)

Comparative Effectiveness:

Head-to-head comparisons are rare. Several attempts have been made to estimate comparative effectiveness through network meta-analysis (NMA).

Five NMA of controlled trials agreed that there were no significant differences in fracture risk among the available drugs.

Adverse Events

Atypical Sub-trochanteric Fractures: An important new potential adverse effect seen in patients treated with bisphosphonates. This comes entirely from observational studies and results are not completely consistent. A systemic review identified 141 women with this fracture and the FDA has issued a warning about the possible link between bisphosphonates and this adverse event. The evidence of a relationship has become more compelling, particularly with longer bisphosphonate use. It is important to know that the absolute risk for atypical fractures is 30- to 100-fold less than the absolute risk of hip fracture among untreated patients at risk. Risk may be higher in patients undergoing longer treatment. Denosumab has also been linked to atypical femoral fractures.

Gastro-intestinal risks: An updated analysis showed increased risk for mild upper GI adverse effects with alendronate, teriparatide, and denosumab. A NMA of 50 RCTs did not find any differences among bisphosphonates. A NM-A found no statistically significant association between oral alendronate or risedronate and risk of subsequent hospitalizations for serious upper GI diagnoses.

Osteonecrosis of the jaw: A review of 23 publications of 2308 cases found that 88% were associated with intravenous bisphosphonates. It has also been reported with use of denosumab.

Others: There is strong evidence that teriparatide may cause headache and hyper-calcenia; zoledronic acid may cause hypo-calcemia and influenza-like symptoms; and raloxifene hot flashes and thrombi-embolic events.

Treatment duration: The FDA found that rate of fractures in patients who received bisphosphonates for more than 6 years was up to 10.6% compared with up to 7.8% for placebo. This questions whether continued bisphosphonates provided additional fracture prevention beyond 5 years.

Dual-Energy X-ray Absorption Monitoring:

Frequent monitoring for osteoporosis may not be necessary, except for women with T-score of -2.0 and lower.

Discussion:

Data about comparative efficacy and effectiveness among therapeutic agents are thin. It is likely that differences between bisphosphonates, denosumab and teriparatide are modest.

Adverse effects differ among drugs. Many are associated with GI effects. Bisphosphonates and possibly denosumab carry the risk for very rare adverse effects: atypical sub trochanteric fracture or osteonecrosis of the jaw.

There is evidence that women with an initial T-score of -1.4 or higher do not benefit from repeated BMD reassessment in less than 15 years. The optimal duration of therapy remains murky, although the evidence suggests that, at least for alendronate, some groups of patients can have the drug safely discontinued after 5 years of treatment.

Among patients receiving FDA-approved drugs for osteoporosis, changes in BMD are not good predictors of anti-fracture effects.

There are many limitations to this review. Head-to head comparisons are scarce. There is a possibility of publication bias and heterogeneity in the definition of outcomes and adverse effects.

Treatment of osteoporosis is an area of very active research.

Annals of Internal Medicine November 18, 2014; 711-22 First author Carolyn J Crandall, David Geffen Scholl of Medicine, University of California, Los Angeles.

a Zoledronic acid: (*Zometa* Novartis) is a bisphosphonate given intravenously. As with all bisphosphonates, it slows bone resorption.

b Denosumab (*Prolia* Amgen): A human mono-clonal antibody which inhibits RANK-Lignad, a protein that acts as the primary signal for bone removal. Precursors of osteoclasts (pre-osteoclasts have surface receptors called RANK. Rank is activated by the RANK-Ligand, which exists as cell surface molecules on osteoclasts. Activation of RANK by RANK-Ligand promotes maturation of pre-osteoclasts into osteoclasts. Denosumab inhibits this maturation by binding to RANK-Ligand, protecting bone from degradation.

c Teriparatide: (*Forteo* Lilly) A recombinant form of parathyroid hormone (1,34 amino acid parathyroid hormone), a portion of the parathyroid hormone. It is an effective anabolic (bone growing) agent. Intermittent use activates osteoblasts more than osteoclasts leading to an overall increase in bone mass. It is the only anabolic (bone growing) agent indicated for use in postmenopausal women with osteoporosis. It is given in microgram amounts subcutaneously once daily. Chronically elevated parathyroid hormone (PTH—84 amino acids) regulates calcium and phosphate metabolism. It increases serum calcium partly by

increasing bone resorption. Chronically elevated PTH depletes bone stores. However, intermittent exposure to PTH will activate osteoblasts more than osteoclasts. Once daily teriparatide has a net effect of stimulating new bone formation.

Teriparatide is the only FDA approved agent for treatment of osteoporosis that stimulates new bone formation. Teriparatide (increasing bone formation) has been combined with denosumab (decreasing bone resorption) and is reported to increase BMD more than either agent alone.

d **Raloxifene: (*Evista* Lilly) an oral selective estrogen receptor modulator (SERM) that has estrogenic actions on bone and anti-estrogen actions on the uterus and breast. It is used for prevention of osteoporosis in post menopausal women.**

Source: Wikipedia.

This is an important application for primary care. I have abstracted the article in detail.

The osteoporosis-fracture literature is massive. Many drugs are available. But we still do not know if there is a "best" one. The length of drug treatment, and if, or how often to check progress of osteoporosis treatment is not certain. Few studies included the very old.

The cost to society and the elderly is great and increasing.

Osteoporosis is only half of the problem of fractures in the elderly. The other half is falling. Both remain challenges.

At present, I would prescribe the least costly drug. And fully inform patients about possible adverse effects.

Prevent osteoporosis as much as possible. It is important to advise patients to maintain good nutrition during the peri-menopause and include optimum intake of vitamin D and calcium.

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11-3 ASSOCIATION BETWEEN THE MEDICARE HOSPICE BENEFIT WITH HEALTH CARE UTILIZATION AND COSTS FOR PATIENTS WITH POOR –PROGNOSIS CANCER
Original Investigation

High intensity medical care at the end-of-life is common. There is increasing consensus that such care can produce poor outcomes and conflict with patient preferences.

The Institute of Medicine report *Dying in America* has drawn attention to the difficulties of providing palliative care. Patients with cancer have the highest rates of hospice enrollment, but the length of stay in hospice is declining, often to less than 3 days.

The Medicare administration monitors hospice with inappropriately long stays. This discourages early admissions that are likely to produce long stays. Medicare does not reimburse physicians for discussing patients' end-of-life preferences. Medicare requires patients to formally renounce curative care before enrollment in hospice. But patients often wish to continue active treatment.

There are concerns that increasing hospice use could increase costs. A key issue is a better understanding of the relationship between hospice and health care utilization, and its implications for costs at end-of-life.

This study used data from Medicare beneficiaries with poor prognosis, and matched data of those enrolled in hospice with those who died without hospice care. Patients receiving cancer-directed treatment during hospice care were excluded.

METHODS

Study Population: From a nationally representative 20% sample of Medicare beneficiaries, identified those with poor prognosis malignancies (lung, pancreas, brain, metastatic, hematological) who died in 2011. All would have been eligible for hospice—available to those with terminal illness and expected survival of less than 6 months. Matched 18 165 hospice patients with 18 165 non-hospice patients.

RESULTS

At baseline, the 2 groups were well matched: mean age 80, median days from poor-prognosis to death 212. More hospice beneficiaries lived in higher income zip codes.

Medium hospice stay was 11 days. Less than 6% of stays exceeded 6 months.

Utilization and Costs in the last year of life: Non-hospice beneficiaries had more hospitalizations mainly for non-cancer conditions. Their rate of intensive care and invasive procedures was higher; 75% died in hospitals or skilled nursing facilities vs 14% for those with hospice. For hospice beneficiaries, in the week before entry, the average daily costs were $146 higher than costs for the non-hospice group. Costs for the hospice group declined rapidly after admission. In the last week of life, daily costs were an average of $556 vs $1203. Longer hospice stay was associated with larger savings. Cumulative costs for hospice in the last year of life were $59 037 vs $71 094 for non-hospice.

	Non-hospice	Hospice	Risk ratio
Hospitalizations %	**65**	**42**	**1.5**
Intensive care admissions %	**36**	**15**	**2.4**
Invasive procedures %	**51**	**27**	**1.9**
Death in hospital or nursing facility %	**74**	**14**	**5.3**
Costs in last year of life $	**71 517**	**62 819**	**Difference 8697**

DISCUSSION

In this matched cohort of Medicare beneficiaries with poor prognosis cancer, there were large differences in care utilization between hospice and non-hospice beneficiaries at the end-of-life.

Hospice patients were hospitalized less, received less intensive care, underwent fewer procedures, and were less likely to die in hospitals and skilled nursing facilities. More non-hospice patients were admitted to hospitals and ICUs for acute conditions not directly related to their poor-prognosis cancer.

Hospice care was associated with substantially lower total medical care costs in the last year of life.

Hospice enrollment of 5 to 8 weeks produced the greatest savings. Shorter stays produced fewer savings.

CONCLUSION

Hospice patients had significantly lower rates of hospitalization, intensive care admission, and invasive procedures at the end of life.

Health care expediters were significantly lower for hospice patients during the last year of life.

JAMA November 2014; 312:1888-96 Original Investigation, First author Ziad Obermeyer, Brigham and Women's Hospital, Boston Mass.

In the past, patients and families were often told "Nothing more can be done". But there is much that can be done: pain control, comforting, spiritual care, family support, dying at home.

Don't wait too long to call on hospice. Sooner is better than later.

At times, family members may disagree about continued aggressive care. This presents an ethical problem. It stresses the importance of patients' giving directions before their final illness (e.g. a

"living will"). Another ethical question: what if patient wishes to continue active treatment, but the physician knows it is useless?

A question which might help decision making is to ask the terminal patients "Are you at peace"?

The Charlotte NC community is blessed by having an excellent hospice and palliative care group. My wife received their home-care for 6 months before dying of colon cancer. This enabled her to die in her own bed, next to me, where she belonged. I have been forever grateful.

11-4 QUALITY AND COSTS OF END-OF-LIFE CARE: THE NEED FOR TRANSPARENCY AND ACCOUNTABILIT

This editorial comments and expands on the previous article.

Am important concern for seriously ill and dying patients is whether the patterns of care, especially receipt of aggressive care, is consistent with patient preferences and improved quality of life. A current dilemma involving the timing of hospice referral is whether it is too late, too early, or just right.

The study raises several important policy issues. If hospice saves money, should health care policy promote increased hospice entry? Do costs and not quality of life predominate at end of life?

The right quality measures are currently not in play. While the majority of hospice programs are of high quality, there is a significant minority for which there are concerns such as discharging hospice patients while they are still living, hospice patients at home who are not visited by professional staff in the last days of life, and for-profit hospice programs that are least likely to provide discretionary or non-core hospice services than non-profit programs.

Dying patients are a vulnerable population and often are impoverished, frail, elderly, and cognitively impaired. As both insurers and Medicare change the financial incentives in health care from doing 'more" to "less" there is increased need for transparency and accountability.

The error of having incorrect quality measures is as serious a concern as policy that focuses solely on expenditures. This is one of the most important lessons from the failed implementation of the Liverpool care Pathway (LP) in England. The LP, which had the original intent of guiding the holistic care of dying persons in an acute care hospital, provided important lessons. The payment of incentives led to a perception that patients were placed on the pathway to enhance the institution's financial well-being rather than the care of the patient. Transparency and accountability were lacking. Bereaved relatives believed that their loved one's death was hastened or that hydration and nutrition were stopped without informed consent. This led to its demise.

That the hospice or hospital-based palliative care teams save money is ethical defensible only if it improves the quality of care and medical decisions are consistent with the informed patient's wishes and goals of care.

Choosing the "just right" timing and setting for hospice care is a complex decision that should include consideration of several factors including, most importantly, the preferences and goals of care of patients and their families. Health care professionals should focus on supporting patients' choices and not be overly influenced by the costs of care or financial incentives tied to the fiscalperformance of health institutions.

JAMA November 12, 2014; 1868-69 Editorial, first author Joan M Teno, Brown School of Public Health, Providence RI

Primary care clinicians must know the reputation of their local hospice. Not all hospices are the same.

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11-5 E-CIGARETTES: The Latest

WHAT IS THE LATEST MARKET INTELLIGENCE ON E-CIGARETTES?

Today there are 466 brands in the market, estimated to be worth more than $2 billion. In January 2014, there were 776 unique flavors on the market. About 2.1 million people in the UK reported regularly using e-cigarettes in 2014, up from 700 000 in 2012. More than half of current or former smokers have tried e-cigarettes.

It has been estimated that in the European Union 23 million smokers, 3.9 million former smokers, and 2.3 million non-smokers had used e-cigarettes in 2012.

WHAT IS THE LATEST EVIDENCE ON WHETHER E-CIGARETTES HELP PEOPLE STOP SMOKING?

A recent widely quoted study showed that smoking e-cigarettes could help some people quit, but that they are no more effective than other forms of nicotine replacement.

IS THERE ANY EVIDENCE THAT E-CIGARETTES ARE A GATEWAY TO TOBACCO PRODUCTS?

Many public health officials are concerned that e-cigarettes

encourage tobacco use by addicting users to nicotine and by making smoking more socially acceptable. Children may be especially vulnerable, as they are at risk of getting hooked on nicotine and then turn to conventional cigarettes. E-cigarettes may also sustain smoking among smokers who might otherwise have quit or may cause former smokers to begin smoking again.

A 2012 study from the US reported that 7% of 11-18 year-olds had used e-cigarettes, up from 3% in 2011. Number of e-cigarettes smoked also rose. .

***JAMA Pediatrics* (2014) reported that adolescents who used e-cigarettes were more likely to smoke conventional cigarettes and less likely to quit smoking. Researchers have labeled e-cigarettes as "gateway devices" that aggravate rather than ameliorate the tobacco epidemic among youth. The CDC (2014) reported many more non-smoking students tried e-cigarettes in 2013 compared with 2011. Non-smoking students who had tried e-cigarettes were twice as likely to say that they intend to smoke conventional cigarettes within the next year compared to those who had never used e-cigarettes.**

HOW ARE E-CIGARETTES CURRENTLY REGULATED?

In the UK, e-cigarettes are regarded as medicines only if they claim to be an aid to reducing or stopping smoking. Another device, known as a nicotine inhaler, rather than an e-cigarette, was granted a medical license in 2014. All other e-cigarettes devices are seen as consumer products that anyone can buy.

Also in the UK, e-cigarettes will be regulated as medicines beginning in 2016, to ensure safety and quality. Then e-cigarettes cannot be promoted to people under age 16, and the packaging and flavoring cannot be designed to attract young people.

The European Parliament passed a law that products containing over 2 mg/mL nicotine need approval as a medicine and the UK will adopt these directives as it stands. (Most e-cigarettes contain less nicotine.) The directive also requires delivery of the same dose with each inhalation and requires monitoring the market for evidence of nicotine addiction and the effect on consumption of traditional cigarettes.

WHAT ABOUT ADVERTISING E-CIGARETTES?

A key complaint from health campaigns is that e-cigarettes are "re-normalizing" and glamorizing "vapinng" by using images that were previously used to promote tobacco smoking. New rules in the UK require that advertizing e-cigarettes should not target people under age 18,

be associated with youth culture, or feature anyone who is, or seems to be, younger than 25. Celebrity advertizing is allowed. Free samples can still be handed out to the public.

The European Tobacco Products directive has banned across border advertising.

WHAT DO THE EXPERTS THINK?

There are 2 camps.

1) The WHO has warned that safety is unproved, and their role in helping people to quit lacks evidence. Some experts have said that e-cigarettes release several toxic substances, including several carcinogens. Nicotine itself is not without harms. Other nicotine replacement products are regarded as medicines. Safety and quality are not guaranteed. Levels of nicotine often do not match those listed on labels and vary from batch to batch. Devices are often poorly manufactured, and contain contaminants. WHO figures show worrying upward trends in e-cigarettes use by younger persons

2) Some smoking cessation specialists argue that e-cigarettes are much safer than conventional cigarettes and that they are rarely used by non-smokers.

AROUND THE WORLD

Brazil, Norway and Singapore have outlawed e-cigarettes completely. New York City has banned use in public places. Retailers in the city are not allowed to sell tobacco products and e-cigarettes to anyone under age 21.

BMJ November 2014 ***BMJ 2014;349:g6444*** **by Zosia Kmietowicz News Editor The BMJ**

No one has claimed that e-cigarettes are healthy.

I believe e-cigarettes are a very bad idea. It was hoped that they would help cigarette smokers quit. They may help some, but more often lead to smoking tobacco cigarettes.

With 466 brands, and 776 flavored, how can we know what we are getting? Some will contain harmful adulterants that they believe may lead more young people to use. Some people will do anything to make a buck.

We do not know all the potential harmful effects of inhaled nicotine. How long did it take to learn the harm of tobacco cigarettes?