Evidence Based Medicine: How to Present the Results of Evidence Based Search

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Introduction

Evidence based medicine (EBM) has many definitions. The most widely cited definition of EBM is adapted from Sackett et al definition of evidence based medicine (EBM). This states that EBM is: "**the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research**" [1].

The definition above highlights the need to draw on both the professional's clinical experiential knowledge and the best external evidence. Neither is enough on its own. As Sackett and his colleagues point out, clinical practices become out of date if new evidence is not drawn upon. However, the clinician must be aware of what evidence is appropriate to integrate into their practice. This can prove to be a difficult and time-consuming task but it is an essential skill in implementing evidence based practice. Health care delivered in ignorance of available research evidence, misses important opportunities to benefit patients and may cause significant harm [2,4]. Providing evidence-based care is recognized as a key skill for health care workers from diverse professions and cultures [5-10]. The ability to deliver evidence-based practice medicine individualization of care and assures the quality of health care for patients today as well as those of tomorrow [11].

Therefore, EBM is not mean (one size fits all) as the globe is diverse in relation to diseases patterns, social values, and economy [12]. Health care should focus on the person, not on problem [13]. A variety of definitions of evidence-based medicine (EBM) have been proposed. However, definitions are in themselves insufficient to explain the underlying processes of EBM and to differentiate between an evidence-based process and evidence-based outcome. The clinical research and EBM are both needed, neither one is perfect [14].

EBM concept relies on three pillars: current best evidence, individual clinical expertise, and the values and desires of the patient. However, evidence best medicine and clinical research are not perfect [14-19]. Evidence interpretation and development of guidelines are different and conflicting by different evaluation groups on the same topics [20]. Thus, sufficient appraising of the available evidence in order to avoid evidence inappropriate interpretation [21-23].

EBM facing many challenges and criticism [24-29]. In developing countries, EBM challenges are deeper than in developed countries. Most of the evidence is imported, for example, the Arab countries production of medical research over eighteen years from 3% of that of United States production [12]. Thus, health care practice depend on evidence that not related to their own research findings and this is not accepted since different society,

culture and even ethnic groups has its unique disease or different same disease forms, different resources and personal qualifications, different responses to therapeutic modalities and different values and patient preferences [12]. Additionally, the skills of critical appraisal are poorly developed among health care professionals [30]. In medical college's curriculum, EBM incorporation is limited [31]. This attribute to adopt unnecessary practice or improper evidence use and may lead to (jerky medicine syndrome) and most of the national guidelines either copied from international ones or unclear or absent [12].

EBM practice is of four steps: formulation of an answerable question (PICO); finding of best evidence; critical appraisal of the evidence and applying the evidence to patient's treatment [32]. The ascending evidence levels are: expert opinion, theories based on physiology, bench top research, and animal studies; case series studies; case control studies; cohort studies; randomized clinical trials and systematic review and meta-analysis [33]. Different clinical questions types require different research types [14]. Randomized clinical trial is the best type of study to answer the question of therapy, diagnosis, prevention and quality improvement. While systematic review/ meta-analysis is the best to answer the question of therapy and diagnosis. Cohort study is suitable to answer question of harm, prognosis, etiology, and prevention. Prognosis question best answered by case-control studies, and case studies. Quality of life and cost-effectiveness questions are best answered by qualitative study and economic evaluation respectively. Prospective study and blind comparison to gold standard are the best studies that give answer to clinical examination question [14]. The evidence graded in to different levels, Table 1 and 2 [33,34].

Table 1. SIGN Grades of evidence [Adapted from SIGN, 33]

Evidence grade	Study type
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 -	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 -	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies; for example, case reports, case series
4	Expert opinion

RCT: randomised controlled trial; SIGN: Scottish Intercollegiate Guidelines Network

Table 2. Evidence levels [Adapted from the Center for Evidence-Based Medicine, Oxford ,34]

Evidence level	Question related to Therapy/ Prevention/ Etiology/ Harm
1a	Systematic reviews (with homogeneity) of randomized controlled trials
1b	Individual randomized controlled trials (with narrow confidence interval)
1c	All or none randomized controlled trials
2a	Systematic reviews (with homogeneity) of cohort studies
2b	Individual cohort study or low quality randomized controlled trials
2c	'' Outcomes'' Research; Ecological studies
3a	Systematic review (with homogeneity) of case control studies
3b	Individual case control study
4	Case- series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or '' first principles''

HOW TO PRACTICE EVIDENCE BASED MEDICIE

Read the following case scenario and apply the steps of EBM process that enable you to help this patient then report your results.

Samira is a patient who recently moved to a new area to be closer to her son and his family. She is 67 years old and has a history of congestive heart failure that was brought on by several myocardial infarctions. She has been hospitalized twice within the last 6 months for worsening of heart failure. At the present time she remains in normal sinus rhythm. She is extremely diligent about taking her medications (enalapril, aspirin and simvastatin) and wants desperately to stay out of the hospital You think she should also be taking digoxin but you are not certain if this would help keep her out of the hospital. You decide to research this question before her next visit.

1. **State you're Focused Clinical Question with the PICO elements: Patient, Intervention, Comparison, and Outcome.**

Question Components	Your Question
P – Patient or Population	Congestive heart failure, elderly
I – Intervention	Digoxin
C – Comparison	Placebo
O – Outcome	Primary: reduce need for hospitalization Secondary: mortality
The well-built clinical question: In elderly patients with congestive heart failure, is digoxin effective in reducing the need for re-hospitalization and reduction in mortality?	

2. Describe where you searched for the evidence and provide the bibliographic information for the 2 articles you found that best address the focused clinical question you.

2.1. For the above clinical question that reflect Huda case history, we have chosen the MEDLINE as a source for searching. The MEDLINE accessed through Pubmed.

2.2. We formulate the following search strategy:

PICO	Our Question	Search Terms
Patient	**Congestive heart failure, elderly**	**Congestive heart failure**
Intervention	**Digoxin**	**Digoxin**
Outcome	**Rate of hospitalization, Mortality**	**Hospitalization, Mortality**

2.3. We search each concept separately.

2.4. We limit the results of the appropriate publication type, language and human.

For Huda case, the question is a therapy question. As we know the best evidence for therapy question is the randomized controlled clinical trial, thus we limit our search to [randomized controlled trial as a publication type. In addition, we select the article published in English language and that evaluated in human being with elderly age.

2.5. Results review.

We found 19 articles that deal with evaluation of Digoxin effectiveness in patients with congestive heart failure [Enclosed]. From them we select number 19 because a detailed analysis of the original DIG studies.

3. Provide a critical appraisal of the articles you found.

Describe the reliability and validity of the evidence you found. Also provide a rating of the strength of the evidence for each article based on the AFP criteria.

Article title:

Ahmad Ali. Digoxin and reduction in mortality and hospitalization in geriatric heart failure: importance on low doses and low serum concentrations. Journal of Gerontology Medical Sciences 2007; 62A:323-329. [35]

Screening	
• **Why was the study done (what was the research question)?**	• **To determine the effect of digoxin at low and high serum digoxin concentration on mortality and hospitalization in congestive heart failure.**
• **Was the study design appropriate?**	• **Yes**
• **Does the study PICO match your question PICO?**	• **Yes**
• **Are there potential conflict of interest issues?**	• **No**

VALIDITY	
F: Patient Follow-Up • Were all patients who entered the trial properly accounted for and attributed at its conclusion (losses to follow-up should be less than 20%)? • Was follow-up complete?	Yes Yes
R: Randomization • Was the recruited patient's representative of the target population? • Was the allocation (assignment) of patients to treatment randomized? • Was the allocation concealed?	Yes Yes Yes
I: Intention to treat analysis • Were patients analyzed in the groups to which they were randomized? • Was all randomized patient data analyzed? If not, was a sensitivity or "worst case scenario" analysis done?	Yes Yes
S: Similar Baseline Characteristics of Patients • Were groups similar at the start of the trial?	Yes
B: Blinding • Were patients, health workers, and study personnel "blind" to treatment?	Yes
E: Equal Treatment • Aside from the experimental intervention, were the groups treated equally?	Yes

Summary of article's validity	
• Notable study strengths or weaknesses or concerns?	**Strength** 1.This is the first comprehensive analysis of the DIG trial that demonstrates that digoxin at low serum digoxin concentration is an effective in older adults as in younger adults suggesting that the pharmacodynamics properties of digoxin are similar regardless of age. However, the pharmacokinetics of digoxin may be more variable at different ages. 2.Kidney function as a major determinant of digoxin excretion had similar effect on serum digoxin concentration regardless of age. 3.Age and digoxin dose were independent predictors of serum digoxin concentration in older adults, suggesting important age related changes in digoxin pharmacokinetics with ageing. 4.There was no age related difference in the incidence of hospitalization due to suspected digoxin toxicity. 5.Low dose Digoxin was the strongest independent predictor of low SDC. Low dose digoxin was associated with low odds of high SDC. **Weakness:** 1.Participants in the DIG trial were predominantly white, male, and relatively younger with mild to moderate heart failure and normal sinus rhythm, thus limiting generalizability. 2.The results of this study are based on post hoc analysis and should be interpreted with caution. However, in the presence of the randomized clinical trial evidence, these provide the best interim evidence of the effect of digoxin on long term broader natural history end points in geriatric patients with heart failure
• How serious are the threats to validity and in what direction could they bias the study outcomes?	With limited effect

CLINICAL IMPORTANCE	
How large was the treatment effect?	Effective [see below notes following table of calculation]
How precise was the treatment effect?	The true risk of the outcome in the population is not known and the best we can do is estimate the true risk based on the sample of patients in the trial. This estimate called the point estimate. We can gauge how close this estimate is to the true value by looking at the confidence intervals [CI] for each estimate. If the CI is fairly narrow then we can be confident that our point estimate is a precise reflection of the population value. The CI also provides us with information about the statistical significance of the result. If the value corresponding to no effect falls outside the 95% CI then the result is statistically significant at the 0.05 level. If the CI includes the value corresponding to no effect then the results are not statistically significant. The finding of this article indicated that mortality rate is significantly [P =0.001 for crude HR, and P=0.017 for adjusted HR] reduced by digoxin in elderly patients with SDC of 0.5-0.9 ng / ml since 95% CI is narrow for HR [0.64-0.9, Adjusted 0.68-0.96], While it is not significantly effective in reducing mortality at SDC level of equal or more than 1 ng/ml. Concerning hospitalization, Digoxin significantly [P= 0.004 to < 0.0001] reduced hospitalization in elderly patients with congestive heart failure in all patients irrespective of SDC levels since 95% confidence intervals are of HR are narrow [for both crude and adjusted HR].

Calculations for mortality:

	Outcome Present	**Outcome Absent**	
Treated/exposed **Digoxin 0.5-0.9 ng/ml** **Digoxin >=1 ng/ml**	**a= 160** **a=188**	**b=312** **b=221**	**EER (Experimental Event Rate) a / a+b** **34** **46**
Control/not exposed	**c=763**	**d=1246**	**CER (Control Event Rate); c/ c+d** **38**

		RRR [RRI] Relative Risk Reduction/Increase %	ARR [ARI] Absolute Risk Reduction/ Increase	NNT [NNH] Numbers Needed to Treat/Harm
CER %	**EER %**	**$\frac{\text{(CER-EER)}}{\text{CER}}$**	**CER-EER**	**$\frac{1}{\text{ARR}}$**
Digoxin 0.5-0.9 ng/ml 38	**34**	**11**	**4**	**25**
Digoxin ≥ 1 ng/ml 38	**46**	**- 21**	**-9**	**-13**

Relative Risk = risk of the outcome in the treatment group / risk of the outcome in the control group

For SDC 0.5-0.9 ng/ml = 34/38 = 0.89

SDC >= 1 ng/ml= 46/38= 1.21

As shown in above, the calculation concerning mortality, this study indicated that:

A. The relative risk [RR], tell us how many times more likely it is that an event will occur in the treatment group relative to the control group. An RR of 1 means that there is no difference between the two groups thus, the treatment had no effect. An RR of less than 1 means that the treatment decreases the risk of the outcome. An RR of more than 1 means that the treatment increased the risk of the outcome. Ln this article, since that RR in patients with SDC of 0.5 – 0.9 is less than 1, the treatment with digoxin in this group of patients is effective in decreases the risk of death. However, in the patients group with SDC of equal or more than 1 ng/ml, the treatment with digoxin do not decrease the risk of death [RR > 1] in patients with this serum level.

B. The absolute risk reduction [ARR] tell us the absolute difference in the rates of events between the digoxin and placebo treatment groups and give an indication of the baseline risk and treatment effect. An ARR of zero means that there is no difference between the two groups and thus, the treatment has no effect. In this study, the absolute benefit of treatment with digoxin is a 40% reduction in death rate for patients for SDC of 0.5-0.9 ng/ml. However, as stated above patients with higher doses of digoxin [SDC >1 ng /ml], the drug not reduced mortality.

C. The relative risk reduction [RRR] is the complement of RR and is probably the most commonly reported measure of treatment effects. It tells us the reduction in the rate of the outcome in the digoxin treatment group relative to that in the placebo treated group. In the selected article the treatment reduced the risk of death by 11 % relative to that in control group in patients with SDC of 0.5 – 0.9 ng/ml. While it is not effective in reducing mortality in patients with SDC of equal or higher than 1 ng/ml.

D. The number needed to treat [NNT] represents the number of patients we need to treat with the experimental therapy in order to prevent 1 bad outcome and incorporates the duration of treatment. Clinical significance can be determined to some extent by looking at the NNTs, but also by weighing the NNTs against any

harms or adverse effects [NNHs] of therapy. In this article, we need to treat 25 patients for two years in order to prevent one death.

Calculation for Hospitalization:

	Outcome Present	Outcome Absent	
Treated/exposed Digoxin 0.5-0.9 ng/ml Digoxin ≥ 1 ng/ml	a=127 a= 135	b=245 b= 274	EER (Experimental Event Rate) 27 33
Control/not exposed	c=703	d=1306	CER (Control Event Rate) 35

CER %	EER %	RRR [RRI] Relative Risk Reduction/Increase % $\frac{(CER-EER)}{CER}$	ARR [ARI] Absolute Risk Reduction/ Increase CER-EER	NNT [NNH] Numbers Needed to Treat/Harm $\frac{1}{ARR}$
Digoxin 0.5-0.9 ng/ml 35	27	23	8	13
Digoxin ≥ 1 ng/ml 35	33	6	2	50

Relative Risk = risk of the outcome in the treatment group / risk of the outcome in the control group

For SDC 0.5-0.9 ng/ml = 27/35 = 0.77

SDC >= 1 ng/ml= 33/35= 0.94

As shown in above, the calculation concerning hospitalization, this study indicated that:

A. In this article, since that RR in patients is less than 1 [SDC of 0.5-0.9 ng/ml, RR = 0.77; SDC of = or > 1 ng/ml, RR=0.94] the treatment with digoxin in this group of patients is effective in decreases the risk of hospitalization.
B. In this study, the absolute benefit of treatment with digoxin is an 80% reduction in hospitalization rate for patients for SDC of 0.5-0.9 ng/ml. However, as stated above patients with higher doses of digoxin [SDC >1 ng /ml], the drug induced 20% reduction in hospitalization rate.
C. In the selected article the treatment reduced the risk of hospitalization by 23% relative to that in control group in patients with SDC of 0.5-0.9 ng/ml. Furthermore, in patients with SDC of equal or more than one ng/ml, treatment with digoxin reduced the risk of hospitalization by 6% relative to that of control.

D. In this article, we need to treat 13 patients for two years in order to prevent one hospitalization for patients with SDC of 0.5-0.9 ng/ml and 50 patients in order to prevent one hospitalization in patients with = or > 1 ng/ml.

Evidence rating: 1 b because this is an extrapolations from level A. The results presented in the selected study are from a reanalysis of an original DIG study [The digitalis investigation group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Eng L Med 1997; 336:525-533; we don't select this trial because it is evaluated in tutorials on the net].

EER (experimental event rate). The proportion of patients in the experimental treatment group who are observed to experience the outcome of interest.
CER (control event rate). The proportion of patients in the control group who are observed to experience the outcome of interest.
ARR (absolute risk reduction). The absolute arithmetic difference in rates of bad outcomes between experimental and control participants in a trial. (This is sometimes called the risk difference.)
RRR (relative risk reduction). The proportional reduction in rates of bad outcomes between experimental and control participants in a trial.
NNT (number needed to treat). The number of patients who need to be treated with the specified intervention to prevent one bad outcome or produce one good outcome over the period of time specified in the study.

4. Summarize the results of the articles you appraised.

4.1. Digoxin and mortality in older patients:

The mortality rate was higher in patients receiving placebo [38%] compared to that receiving digoxin [34%] with low SDC [HR=0.76; 95% CI =0.64-0.9; p=0.001] and lower to that in patients with high SDC [HR=1.13; 95% CI =0.96-1.32; P=0.136]. Multivariable adjustment for baseline covariates did not significantly alter these associations of low and high SDC with mortality.

4.2. Digoxin and hospitalizations in older patients:

Compared with 35% of patients receiving placebo, 27 % with low SDC [HR=0.66; 95%CI=0.54-0.79; P<0.0001] and 33% with high SDC [HR=0.75; 95%CI=0.62-0.91; P-0.004] were hospitalized due to worsening heart failure. Multivariable adjustment for baseline covariates did not significantly alter this association of low and high SDC with heart failure hospitalization.

4.3 Hospitalization due to digoxin toxicity:

During the entire follow-up, 35 [1.2%] patients > 65 years were hospitalized due to suspected digoxin toxicity [Chi –square, P=0.441]. Among older patients, compared with 1% receiving placebo, 1.3% with low SDC [HR=1.15; 95%CI=0.46-2.87; P=0.76] and 2.2% with high SDC [HR=2.12; 95%CI=0.97-4.66; P=0.061] were hospitalized for suspected digoxin toxicity.

4.4 **In patients with age** of > 65 years, age [OR=0.7; 95%CI=0.53-0.94; P=0.016], impaired renal function [OR=0.45; 95%CI=0.33-0.61; P<0.0001] and pulmonary congestion [OR=0.55; 95%CI=0.38-0.81; P<0.0001] were independent negative predictors of low SDC. Low dose digoxin was the strongest independent predictor

of low SDC. In these patients, low dose digoxin was associated with lower odds of high SDC [adjusted OR=0.42; 95%CI=0.30-0.61; P<0.001]. Low dose digoxin was the strongest predictor of low SDC [OR=2.37; 95%CI=1.65-3.39; P< 0.0001].

5 . Discuss the practice implications of the results.

1.Can the results be applied to my patient care? • Is our patient so different from those in the study that its results can not apply? • Patients similar for demographics, severity, co-morbidity and other prognostic factors? • Compelling reason why the results should not be applied?	Yes No, Include patients of > 65 years old with congestive heart failure. Yes No
2.Is the treatment feasible in our setting?	Yes it is available but must explore with patient if she is willing to take it.
3.Were all clinically important outcomes considered	Yes
4.Are the likely treatment benefits worth the potential harms and coasts?	Probably Yes Given NNT 25 to prevent one mortality NNT 13 to prevent one hospitalization.
5.Do we and our patient have a clear assessment of their value s and preferences?	Need to explore with patient

Digoxin is the oldest heart failure drug and is also inexpensive. It is FDA approved for heart failure use and is recommended by HF guidelines [36,37]. However, recent evidence suggests that the use of digoxin in HF has declined [38,39]. Although the reasons for this decline are complex and have not been well studied, it is suspected that the age of DIG trial in the pre-beta-blocker era and lack of mortality benefit of digoxin tempered enthusiasm for digoxin use in today's HF patients. However, there is no evidence that beta-blockers recommended for systolic HF are beneficial in diastolic HF [36,40,41] and about half of all systolic HF do not receive beta-blockers [38,39]. There is also evidence3 that digoxin and beta-blockers are beneficial in the presence of each other [42]. Finally, many elderly HF patients remain symptomatic despite therapy with ACE inhibitors and beta-blockers. Therefore, digoxin can play an important role in reducing HF hospitalization in older adults with symptomatic HF [43,44] and thus improve quality of life and ease the burden on health care system. However, digoxin is used in low doses and care is taken to achieve low SDC, digoxin may also reduce all cause mortality and all cause hospitalizations.

Results of the DIG trial showed that adding of digoxin to standard heart failure therapy had no effect on mortality. However, adding digoxin decreased hospitalizations related to heart failure and improved symptoms in patients treated for heart failure [45]. Reanalysis of the trials findings [this article] have raised new questions about the role of digoxin in heart failure treatment [35]. These new analyses showed that low serum digoxin concentrations used in patients with more severe disease offered the most benefit. Digoxin use in women was associated with increased mortality risk [46]. The reason for this is unclear. This finding should be interpreted with caution, however, because it was based of retrospective data, and the cause of this phenomenon has not been fully elucidated. Prospective clinical trials are needed to determine the serum digoxin therapy for women. The instances of suspected digoxin toxicity and hospitalization were similar in men and women. [47]. Although there was inadequate number of women in the DIG trial to determine whether a specific serum digoxin concentration range was beneficial, or at least did not increase mortality, it is premature to conclude that digoxin should never be used in women [45]. It seems reasonable to initiate digoxin therapy in women only when they clearly symptomatic despite receiving maximal treatment with more proven agents such as diuretics, ACE inhibitors as Huda case indicated. In addition, in a recent analysis of DIG trials [demonstrated that among women with HF, SDC of ≥1.2 ng/ml was associated with increased risk of deaths and that SDC 0.5-1.1 ng/ml was associated with decreased risk of HF hospitalization. These beneficial effects of lower SDC were significant among women with EF <35%, but not in those with EF ≥35%. These findings suggest that women with HF and EF<35% may benefit from digoxin if care is taken to maintain the SDC between 0.5 and 1.1 ng/dl.

State your conclusions or answer to your focused clinical question:

We conclude that digoxin at low SDC was associated with a reduction in mortality and hospitalization in chronic geriatric congestive heart failure and a low dose digoxin was the strongest predictor of low SDC.

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