REVIEW ARTICLE

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Biochemical Monitoring of Patients Treated with Antihypertensive Therapy for Adverse Drug Reactions

A Systematic Review

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Contents

Abstract

Biochemical monitoring of patients treated with antihypertensive therapy is recommended in order to identify potential adverse reactions to treatment. We aimed to review the literature investigating the nature of biochemical monitoring in adults treated in primary care with antihypertensive drugs. Specifically, we wished to establish (i) the proportion of patients with biochemical baseline testing prior to the initiation of antihypertensive therapy; (ii) the proportion of patients with biochemical monitoring after initiation of antihypertensive therapy; (iii) the patient characteristics associated with biochemical monitoring; (iv) the frequency of biochemical monitoring after the initiation of antihypertensive therapy; and (v) the relationship, if any, between biochemical monitoring and adverse patient outcomes.

We searched MEDLINE, EMBASE and Google Scholar from 1948 to 31 December 2010 using a combination of text words and search terms.

Retrospective and prospective cohort studies, cross-sectional studies, randomized controlled trials or quasi-randomized controlled trials, and audits of current clinical practice were included. Clinical trials, case reports and case series were excluded. Studies were included if they provided data on the proportion of patients treated with antihypertensive therapy in primary care who had any biochemical monitoring before or after the initiation of therapy. In total, 15 studies were included in our review, which used a wide variety of definitions of monitoring prior to and after the initiation of antihypertensive therapy. From 17% to 81% of patients treated with antihypertensive drugs had a baseline biochemical test and from 20% to 79% had any follow-up monitoring. In only 7 of the 12 studies that examined follow-up monitoring did more than half of the patients have any monitoring.

Overall, this systematic review provides evidence that monitoring as recommended by published guidelines is not commonly undertaken. Only two studies were identified that examined patients with both baseline testing and follow-up monitoring. Omission of one or the other limits the ability to analyse the effect of treatment on electrolyte concentrations or renal function. There is limited research on the patient factors associated with monitoring and further work is required to determine the impact of monitoring on adverse patient outcomes. Important barriers to effective monitoring exist and this review emphasizes that these have not yet been overcome.

Antihypertensive therapy is commonly used in primary care but can cause a range of adverse drug reactions (ADRs), including electrolyte disturbances such as hyperkalaemia, hypokalaemia, and hyponatraemia.[1] Biochemical monitoring can identify changes related to potential adverse reactions to treatment.[2,3] This is especially important for adverse reactions that have generally few or non-specific symptoms, but potentially serious consequences, such as hypokalaemia.[4]

Guidelines recommend that patients with newly diagnosed hypertension should have baseline biochemical tests of renal function and electrolyte concentrations prior to starting antihypertensive treatment, and follow-up monitoring after starting treatment, and at intervals following any dose changes.[5-8] However, the primary evidence supporting these monitoring recommendations is limited.[9] For example, guidelines for the monitoring of serum potassium concentration have been described as 'at best makeshift and often drawn from the know-how of the treating physician'.[10]

It is not well known to what extent published guidelines on monitoring of patients for adverse reactions to antihypertensive therapy are followed in primary care. We wished to identify and summarize the literature investigating the nature of biochemical monitoring in adults treated in primary care with antihypertensive therapy. Specifically, we wished to establish (i) the proportion of patients with biochemical baseline testing prior to the initiation of antihypertensive therapy; (ii) the proportion of patients with biochemical monitoring after initiation of antihypertensive therapy; (iii) the patient characteristics associated with biochemical monitoring; (iv) the frequency of biochemical monitoring after the initiation of antihypertensive therapy; and (v) the relationship, if any, between biochemical monitoring and adverse patient outcomes.

1. Search Strategy for the Identification of Studies

Two electronic databases – MEDLINE (from 1948) and EMBASE (from 1980) – were searched up to 31 December 2010 using the OVID interface to identify studies for potential inclusion. We used a combination of text words and controlled vocabulary search terms for MEDLINE (MeSH)

and EMBASE (EMTREE) [see Appendix 1, Supplemental Digital Content (SDC), http://links.adisonline.com/DSZ/A53]. The search was carried out with no language restrictions. Once duplicates were removed from the combined databases, studies were selected for inclusion based on the study title and abstract. Google and Google Scholar were also searched using a combination of search words (Appendix 2, SDC) in order to identify unpublished literature and studies published in journals not indexed by MEDLINE or EMBASE. When studies appeared to meet the inclusion criteria or where a decision could not be made based solely on title or abstract, full-text copies were obtained.

1.1 Citation Searching

Articles that cited or were cited by the included studies were also screened in order to identify any further relevant studies. Additionally, reference lists from important reviews were searched and personal files were examined in order to identify further studies.

1.2 Inclusion Criteria

The following criteria were applied in the selection of studies.

1.2.1 Types of Studies

We included randomized controlled trials or quasi-randomized controlled trials investigating the impact of various interventions on monitoring, retrospective and prospective cohort studies, cross-sectional studies, and audits of current clinical practice. The results from the control arm of a randomized trial were used when comparisons were made with other studies. Clinical drug trials were excluded because they do not accurately reflect monitoring in a normal treatment setting. Case reports and case series were also excluded.

1.2.2 Types of Patients

Male and female adults with hypertension treated with antihypertensive therapy outside the hospital or clinical trial setting were included. No upper age limit was applied.

1.2.3 Types of Biochemical Monitoring

The biochemical monitoring tests identified for inclusion were tests of serum creatinine, urea, sodium and potassium concentration.

1.2.4 Types of Outcome Measures

The primary outcome measure was the proportion of patients with any biochemical testing prior to the start of treatment or any follow-up monitoring. The secondary outcome measures were the frequency of tests (number of tests over a period of time), patient factors associated with biochemical testing at baseline or follow-up monitoring, and any additional information reported on baseline testing or biochemical monitoring.

1.3 Methods of the Review

Data extraction was carried out using a standardized data extraction form (Appendix 3, SDC). The primary outcome measure – the proportion of patients with any biochemical testing or follow-up monitoring – was compared between the included studies. The studies were also critically appraised based on five quality and seven methodological indicators. The quality indicators were developed using the Newcastle-Ottawa Quality Assessment Scale[11] as a guide.

2. Findings

We searched MEDLINE and EMBASE without any language restrictions, using a combination of medical subject headings and text words. The initial search strategy retrieved 1265 unique citations (figure 1). Ninety-four studies were selected based on their title and abstract, and full-text copies were retrieved. Six studies were identified through hand searching.[12-17] One randomized study that examined interventions for increasing laboratory monitoring was excluded as, although it did provide data on the proportion of patients monitored both pre- or post-intervention, it did not provide discrete data on patients treated solely with antihypertensive therapy.[16] Three studies were also later excluded as they presented only data on the proportion of dispensed prescriptions or patient visits with biochemical monitoring, and

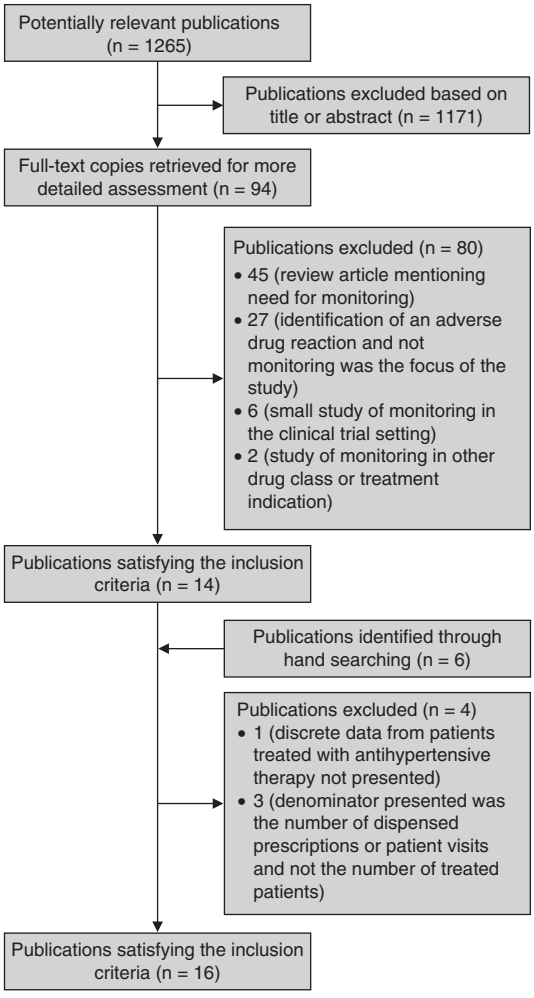

Fig. 1. Flowchart of selection of studies into systematic review.

not the proportion of patients.[14,15,17] One study was published in two halves, therefore 15 studies from 16 publications were included in the final review (Appendix 4, SDC).

The UK, France and the US provided the majority of the studies and all but two of the studies[18,19] were cross-sectional or retrospective analyses of monitoring. All of the studies used databases of electronic prescription records to identify the patients treated with antihypertensive therapy. The majority of studies (80%) used electronic records to identify laboratory tests, with one study undertaking an assessment of the ability of the administrative data to identify monitoring. Raebel and colleagues[20] selected a random sample of patients and compared the monitoring results from the administrative database with actual patient records, which were considered the gold standard, to determine the sensitivity and predictive values of the administrative data.

Most studies (67%) were undertaken using insurance databases to identify a range of patients typically treated with antihypertensive therapy in primary care. Some studies focused on specific subgroups of patients, including the elderly[21,22] or those with diabetes mellitus.[23] Four studies were carried out in patients newly treated with antihypertensive therapy.[19,23-25] The majority of studies focused on follow-up monitoring, with three studies examining only baseline testing.[19,22,26] Seven studies[12,23-25,27-29] reported data on the proportion of patients with baseline biochemical testing and follow-up monitoring therapy, of which two[25,27] presented data on the proportion of patients with both testing before and monitoring after the initiation of antihypertensive therapy.

2.1 Summary of the Primary Outcome Measure

The proportion of patients with biochemical testing prior to the initiation of therapy varied by the timeframe used, the antihypertensive drug class and the serum concentration measured. From 17% to 81% of patients treated with antihypertensive drugs had a baseline biochemical test (table I). There was also a 4-fold range in the proportion of patients with follow-up monitoring (from 20% to 79%) [table II]. In 5 of the 12 studies examining follow-up monitoring, fewer than half the patients had any evidence of biochemical monitoring.

2.2 Summary of Secondary Outcome Measures

Nine studies presented information on patient characteristics associated with either baseline testing or follow-up monitoring. Biochemical testing prior to the initiation of treatment was less likely in women,[22,25] and in patients with fewer comorbidities.[22] Few studies presented additional

information besides the proportion of patients with baseline testing or follow-up monitoring.

Increasing age,[20,21,23,25,27,30] greater number of concomitant prescriptions,[23,27] and increasing number of co-morbidities such as diabetes[20,25,30] or chronic renal failure[20,23] are significantly associated with follow-up monitoring. One study demonstrated that patients prescribed thiazide diuretics were more likely to have their serum electrolytes monitored than those prescribed angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists or calcium-channel antagonists.[24] Conversely, another study demonstrated that patients treated with ACE inhibitors were more likely to have monitoring than those treated with thiazide diuretics.[25] Patients with fewer outpatient encounters and those travelling longer distances to receive treatment were significantly less likely to have follow-up monitoring.[12] Some studies have demonstrated that male

Table I. Proportion of patients with baseline testing (grouped by the definition of baseline testing)

Study (year)	Antihypertensive drug treatment	What to test?	Patients with baseline testing (%)
3 months prior			
Kalra et al.[29] (1999)	ACE inhibitors	Creatinine	45
6 months prior to and 14 days after			
Simon et al.[22] (2005)	ACE inhibitors	Creatinine or potassium	67
Simon et al.[22] (2005)	AT-II receptor antagonists	Creatinine or potassium	72
Simon et al.[22] (2005)	Diuretics	Creatinine or potassium	67
Lafata et al.[19] (2007)[a]	ACE inhibitors, AT-II receptor antagonists	Creatinine and potassium	59
Lafata et al.[19] (2007)[a]	Diuretics	Potassium	55
6 months prior			
McAlister et al.[24] (2007)	Thiazide diuretics	Sodium or potassium	21
McAlister et al.[24] (2007)	Thiazide diuretics	Creatinine	32
McAlister et al.[24] (2007)	ACE inhibitors, AT-II receptor antagonists, β-adrenergic receptor antagonists (β-blockers), calcium channel antagonists	Sodium or potassium	23
McAlister et al.[24] (2007)	ACE inhibitors, AT-II receptor antagonists, β-blockers, calcium channel antagonists	Creatinine	36
Besançon et al.[26] (2008)	Spironolactone and ACE inhibitors	Potassium and creatinine	30
1 year prior and 2 days after			
Coleman et al.[25] (2010)	Antihypertensives	Creatinine	46
Coleman et al.[25] (2010)	Antihypertensives	Urea	38
Coleman et al.[25] (2010)	Antihypertensives	Sodium	43
Coleman et al.[25] (2010)	Antihypertensives	Potassium	42
Coleman et al.[25] (2010)	Antihypertensives	Any laboratory test	47
2 years prior			
Clayton et al.[27] (2006)	Thiazide diuretics	Sodium and/or potassium	17
Unclear			
Rhodes[28] (1992)	Diuretics	Urea or electrolytes	11
Kalra et al.[29] (1999)	ACE inhibitors	Creatinine	49
Sauer et al.[12] (2006)	ACE inhibitors or AT-II receptor antagonist	Potassium and creatinine	81

a Only data from the control arm in patients who were new medication users are presented.

ACE = angiotensin-converting enzyme; **AT-II** = angiotensin-II.

Table II. Proportion of patients with follow-up monitoring (grouped by the definition of follow-up monitoring)

Study (year)	Antihypertensive drug treatment	What to test?	Patients with follow-up monitoring (%)
2 weeks after			
Sauer et al.[12] (2006)	ACE inhibitors or AT-II receptor antagonist	Potassium and creatinine	27
4 weeks after			
Sauer et al.[12] (2006)	ACE inhibitors or AT-II receptor antagonists	Potassium and creatinine	33
3 months after			
Kalra et al.[29] (1999)	ACE inhibitors	Creatinine	29
Sauer et al.[12] (2006)	ACE inhibitors or AT-II receptor antagonists	Potassium and creatinine	50
6 months after			
Coleman et al.[25] (2010)	Antihypertensives	Creatinine	35
Coleman et al.[25] (2010)	Antihypertensives	Urea	30
Coleman et al.[25] (2010)	Antihypertensives	Sodium	34
Coleman et al.[25] (2010)	Antihypertensives	Potassium	34
Coleman et al.[25] (2010)	Antihypertensives	Any laboratory test	36
1 year after			
Hurley et al.[13] (2005)	ACE inhibitors	Creatinine	65
Hurley et al.[13] (2005)	ACE inhibitors	Potassium	60
Raebel et al.[20] (2007b)	ACE inhibitors	Creatinine and potassium	68
Raebel et al.[20] (2007b)	AT-II receptor antagonists	Creatinine and potassium	74
Géradin-Marais et al.[21] (2008)	Diuretics	Serum chemistry monitoring	75
Hurley et al.[13] (2005)	Diuretics	Creatinine	64
Hoch et al.[18] (2003)	Diuretics	Potassium	79
Hurley et al.[13] (2005)	Diuretics	Potassium	66
Rhodes[28] (1992)	Diuretics	Urea or electrolytes	20
Raebel et al.[30] (2007a)	Spironolactone	Creatinine and potassium	72
McAlister et al.[24] (2007)	Thiazide diuretics	Sodium or potassium	38
McAlister et al.[24] (2007)	Thiazide diuretics	Creatinine	41
McAlister et al.[24] (2007)	ACE inhibitors, AT-II receptor antagonists, β-blockers, calcium channel antagonists	Sodium or potassium	31
McAlister et al.[24] (2007)	ACE inhibitors, AT-II receptor antagonists, β-blockers, calcium channel antagonists	Creatinine	42
2 years after			
Clayton et al.[27] (2006)	Thiazide diuretics	Sodium and/or potassium	32
Unclear			
Kalra et al.[29] (1999)	ACE inhibitors	Creatinine	62
Raebel et al.[23] (2010)	ACE inhibitors, angiotensin-II receptor blockers, spironolactone	Potassium	71

ACE = angiotensin-converting enzyme; **AT-II** = angiotensin-II.

patients were significantly more likely to have follow-up monitoring;[20,27,30] however, two studies found that female patients were likely to be monitored[21,23] and another found no sex difference.[25]

Three studies presented additional information on the number of monitoring tests, demonstrating a low frequency of monitoring subsequent to the initial first test. Clayton and colleagues[27]

provided data on the number of follow-up electrolyte tests, in addition to data on the proportion of patients with follow-up monitoring. McAlister and colleagues[24] presented the test density (number of tests per 100 patients per 6 months) by drug class, with elderly patients treated with thiazide diuretics having the greatest density of tests. Coleman and colleagues[25] reported a low mean number of repeat monitoring tests (1.4), with patients started with an ACE inhibitor or a potassium-sparing diuretic having the greater mean number of tests.

Two studies examined the relationship between monitoring and adverse patient outcomes. In a subgroup of diabetic patients treated with antihypertensive therapy, serum potassium monitoring was associated with a decreased risk of hyperkalaemia and hyperkalaemia-associated adverse events such as emergency department visits, hospitalization and death.[23] In a larger group of patients treated with a broader range of antihypertensive therapy, monitoring of renal function or electrolyte concentrations was significantly associated with hospital admission and discontinuation of antihypertensive treatment.[31] No association between biochemical monitoring and patient death was identified.

The studies differed significantly when compared on five quality and seven methodological indicators (Appendices 5 and 6, SDC).

3. Discussion

This systematic review identified a range of studies examining the nature of monitoring for ADRs in patients treated with antihypertensive drugs. The estimated rate of baseline biochemical testing in primary care varied markedly, from 17% to 81%.[12,19,22,24-29] Similarly, the proportion of patients with follow-up monitoring ranged from 20% to 79%.[12,13,18,20,21,23-25,27-30] These wide ranges reflect the variation in methods and definitions of monitoring used by the different studies. This variability and the differing study populations make comparison between studies difficult.

While the majority of studies included patients as young as 18 years of age, three were carried out exclusively in older patients.[21,22,24] These three studies demonstrated high rates of monitoring, which may reflect more targeted monitoring of a population in which adverse reactions to drug treatment are more frequent. Four studies[19,23-25] presented data on monitoring in newly treated patients, who may differ from patients who have been treated for some time (e.g. co-morbidities, severity of hypertension, demographics). This has important implications for monitoring as patients who are newly treated may be particularly vulnerable to ADRs as they are drug-naïve, and some ADRs, such as hyponatraemia, have been shown to be most common very soon after the initiation of treatment.[32,33] The studies by Kalra et al[29] and Bootsma et al.[34] found that doctors substantially overestimate the proportion of patients in whom they monitor biochemical parameters.

The majority of the studies identified by the review assessed the nature of monitoring using large insurance or administrative databases. The nature of laboratory monitoring in these large organizations may be significantly different from that carried out in other countries and in other healthcare organizations. Only one study undertook any analysis to quantify the ability of the administrative data to identify monitoring.[20]

All of the studies described biochemical monitoring as an important tool for identifying adverse reactions to treatment. However, over one-quarter of the studies made no reference to a published guideline on monitoring patients for adverse reactions to antihypertensive therapy.

Most of the studies focused exclusively either on baseline testing or follow-up monitoring. Only two studies examined the important relationship between baseline testing and monitoring following the initiation of treatment. The majority of studies only treated monitoring (either baseline testing or follow-up monitoring) as a binary outcome. Indeed, only three studies provided any additional information on the frequency of monitoring,[24,25,27] which limits any analysis on the nature of monitoring.

Several studies only presented the prevalence of monitoring and did not provide any information on the patient factors associated with monitoring, which limits the interpretation of their results.[13,18] Finally, only two studies[23,31] exam-

ined any relationships between the monitoring of patients and adverse outcomes. Monitoring is advocated as a way of preventing patient harm but little to no information was presented in previous studies on the relationship between monitoring and adverse patient outcomes.

3.1 Barriers to Monitoring

Monitoring is generally recommended as a tool for the identification of potential adverse reactions to therapy. However, evidence obtained from the studies identified by this systematic review suggests that as many as one patient in five does not obtain any follow-up monitoring during treatment with antihypertensive therapy. Although doctors have described monitoring as a critical component of their practice, they also view it as a time-consuming process.[35]

A major barrier to monitoring is the lack of commonly accepted and implementable guidelines. Certainly, when doctors were interviewed on their perceptions of laboratory monitoring, many felt that there were no universally accepted recommendations for the frequency of laboratory monitoring.[35] This uncertainty can lead doctors to making decisions on monitoring based on their clinical experience rather than evidence or guidelines, which may in turn create opportunities for adverse events. Some published guidelines are vague and describe monitoring as a 'routine investigation'[36] or that 'attention' for an ADR such as hyperkalaemia is necessary.[37] A small number of guidelines are far more detailed, with recommendations for biochemical testing prior to the initiation of therapy, specific details for the frequency of follow-up monitoring and actions to be taken should the laboratory tests be outside a certain range of values.[5,38] The most detailed recommendations on the frequency of monitoring and when to stop treatment are often provided in the guidelines for the treatment of hypertension in patients with chronic kidney disease.[39-41] However, the guidelines fail to demonstrate that they are effective or cost effective in preventing drug-induced harm. Drug manufacturers also provide some information on monitoring for ADRs in the Summary of Product Characteristics (SPC) – a regulatory document – for each drug. However, the information on monitoring for ADRs in SPCs is often vague and inadequate in that it does not provide enough information to carry out any monitoring or act on the results.[42]

Other barriers to monitoring have been described, including uncertain responsibility for monitoring, patient non-adherence, and absence of alerts or reminders to monitor.[35] Most patients with hypertension, especially those with 'simple' hypertension, are treated in the community, and the general practitioner who initiated treatment would usually be responsible for monitoring. However, in instances where treatment is initiated by specialist prescribers outside of primary care, it may be difficult to determine where the responsibility for monitoring lies. Non-adherence to monitoring by patients may also be a concern, where patients fail to attend for monitoring scheduled by the general practitioner. Another potential barrier to monitoring is the lack of well designed and implementable electronic alerts to remind the practitioner of the need to undertake monitoring both pre- and post-initiation of therapy, as well as alerts to indicate that a patient had not attended for monitoring.

3.2 Strategies for Improving Monitoring

Several interventions have been recently developed to encourage biochemical monitoring, including academic detailing,[19] electronic laboratory monitoring alerts within a computerized medical records system,[15-18,43] an automated voice message to the patient[16] and a pharmacy team outreach to the patient.[16] The use of electronic alerts and reminders targeted at doctors using information technology in daily practice may go some way towards improving laboratory monitoring. Indeed, when respondents to an electronic Delphi survey were asked to form a consensus on the most important features of general practice computer systems for the improvement of patient safety, all agreed on the importance that "it should be possible to set up the [computer] system so that patients can be automatically recalled for blood tests and other forms of monitoring".[44] However, there is the possibility that the

problem of alert fatigue may reduce the effect of the reminders. Alert fatigue may occur when the alerts recommending monitoring do not relate to sufficiently serious outcomes or are irrelevant, or because a given alert appears repeatedly. In these circumstances the alert may be overridden or simply ignored.[45-48] Although some slight improvement in the rates of appropriate biochemical monitoring have been observed following the introduction of interventions to improve monitoring, most were not statistically significant.[49,50] The results obtained from the studies investigating the various interventions are also limited as the majority of these studies have been undertaken in US healthcare systems and therefore the results may not be generalizable to other environments.

3.3 Future Work

Guidelines recommend biochemical monitoring to prevent harm from adverse reactions to treatment, although there are significant differences in the nature and level of detail of published recommendations. There is undoubtedly a need to develop commonly accepted and implementable guidelines. However, these differences in published recommendations for monitoring are largely the result of the lack of primary evidence. Previous studies have focussed primarily on describing the nature of monitoring and none has established an evidence basis for a rational and reasonable monitoring scheme. In an ideal hypothetical experiment, biochemical monitoring of patients would occur as frequently as feasible (e.g. once a week) in order to identify potential ADRs. Observations could then be deleted in order to compare the specificity or specificity of the different monitoring regimens (e.g. monitoring every week vs monitoring every 4 weeks). For example, if 90% of all pre-specified ADRs were identified by monitoring every week, compared with 87% of ADRs that were identified by monitoring every month, this would suggest that the benefit from monitoring every week compared with every month would be slight.

There have been no efficient developments in electronic systems to alert doctors when a patient has not had a laboratory test that the doctor had recommended, although doctors would welcome this.[51] Finally, no work has been undertaken to investigate patients' perceptions on laboratory monitoring. The large proportion of patients who did not have follow-up monitoring following the initiation of their antihypertensive treatment may have been the result of patients failing to attend for laboratory testing, rather than failure of doctors to order the tests. Goldman and colleagues[35] suggested that further work should investigate how doctors communicate the need for laboratory monitoring with patients and how patients perceive the role of monitoring in the detection and potential prevention of harm. Interventions that involve the patients in the monitoring process (e.g. through the use of automated phone calls to patients due for drug monitoring) show significant improvement in the frequency of follow-up monitoring.[16] Future work should investigate ways to improve the awareness of the importance of recommended monitoring in patients.

Monitoring of patients for adverse reactions to treatment should be cost-proportionate, in that the cost of testing should not be greater than the cost savings associated with reducing the health burden of adverse reactions to therapy. The only study to examine this used a probabilistic decision model to compare the cost of laboratory monitoring programme for patients treated with ACE inhibitors or angiotensin-II receptor antagonists with the cost of the adverse outcomes of hyperkalaemia and acute renal failure.[52] On average, the programme cost evaluated in 2009 was $24 extra per person, per year. Cost savings were only observed when the analysis was restricted to the monitoring programme targeted to patients who are at higher risk of adverse events. Although the results are not generalizable outside of the system within which the analysis was undertaken – a US health maintenance organization with an established electronic health record system – the results do suggest that for laboratory monitoring of patients treated with antihypertensive therapy to be cost effective, the monitoring needs to be carried out in a population with a high risk of adverse events.

4. Conclusions

This systematic review identified several large, well planned studies that examined the prevalence of monitoring and identified patient factors associated with greater rates of monitoring. However, very few studies examined both baseline testing and follow-up monitoring. The majority of studies demonstrated that monitoring is not being carried out in accordance within published guidelines. In only 58% of the studies examining follow-up monitoring did more than half of the patients having any monitoring. There also remains a significant gap in knowledge with respect to the patterns of monitoring of antihypertensive drugs for ADRs in newly diagnosed and newly treated hypertensive patients. Further research that accurately examines potential relationships between monitoring and adverse patient outcomes is important in order to determine the effectiveness and value of monitoring. Several important barriers to effective monitoring have been described, but our study emphasizes that these have yet to be satisfactorily overcome.

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