



TITLE: Transcatheter Aortic Valve Implantation for Aortic Stenosis: A Review of the Clinical Effectiveness and Guidelines

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CONTEXT AND POLICY ISSUES

Transcatheter aortic valve implantation (TAVI) was developed as an alternative for patients with severe aortic stenosis that require aortic valve replacement but who are not eligible for conventional surgical aortic valve repair (SAVR).^{1,2} Approximately 300,000 people worldwide have been diagnosed with this condition, and approximately one third of them are considered too risky for open heart surgery.³ Currently, the two most common approaches for TAVI are transfemoral and trans-apical procedures.⁴ There are two commercially available systems for TAVI: Edwards Sapien (LifeSciences, Irvine, CA, USA) and CoreValve (Medtronic, Minneapolis, MN, USA).⁴ The Edwards Sapien system was approved for use by Health Canada in 2001 for the transfemoral approach,⁵ and the CoreValve system is available in Canada through the Special Access programme.³ Further context and policy issues were summarized in a CADTH report in 2010 titled "Percutaneous Heart Valve Replacement for Valvular Heart Disease: A Review of the Clinical Effectiveness, Cost-effectiveness, and Guidelines".⁶

This report will provide a review of the clinical effectiveness and guidelines for the use of transcatheter aortic valve implantation for aortic stenosis, through trans-femoral and trans-apical routes.

RESEARCH QUESTIONS

1. What is the clinical effectiveness (including documented mortality reduction) of transcatheter aortic valve implantation in adult patients with aortic stenosis who are ineligible for cardiac surgery?
2. What is the clinical evidence regarding different possible procedural access points for transcatheter aortic valve implantation?
3. What is the clinical evidence regarding long-term success and complication rates associated with transcatheter aortic valve implantation?

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4. What are the evidence-based guidelines and criteria regarding selection of optimal candidates for transcatheter aortic valve implantation?

KEY MESSAGE

Limited evidence showed that trans-catheter aortic valve implantation has statistically significant clinical benefits compared to standard therapy or conventional surgical aortic valve repair. Long-term success and complication rates of the procedure are uncertain. Strict patient and procedural access selection are critical for a successful trans-catheter aortic valve implantation procedure.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Medline, Embase, PubMed, The Cochrane Library (2011, Issue 9), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 01, 2005 and September 27, 2011.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	Adults patients with severe and likely inoperative aortic stenosis
Intervention	Transcatheter aortic valve implantation (trans-femoral and trans-apical routes)
Comparator	Any comparator. Comparators may include traditional surgical aortic valve stenosis treatment
Outcomes	Clinical effectiveness, mortality reduction, long-term (3 to 5 year) success rates, safety, quality of life, competency, optimal device and procedural approach, patient selection guidelines and criteria (patient scoring, age range, which type of professional can select [cardiologist, cardiac surgeon, interventionist])
Study designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to 2005, or if they were duplicate publications of the same study.

Critical Appraisal of Individual Studies

The quality of the included systematic reviews, randomized controlled trials, and guidelines was assessed using AMSTAR,⁷ Downs and Black,⁸ and AGREE⁹ checklists, respectively. The quality of the included studies is summarized in Appendix 3.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 538 citations, and 23 additional studies were identified by searching the grey literature. After screening of abstracts, 82 potentially relevant studies were selected for full-text review. One National Institute for Health and Clinical Excellence (NICE) systematic review,¹⁰ two randomized controlled trials (RCTs)^{11,12} and two evidence-based guidelines^{13,14} were selected for inclusion. Appendix 1 describes the PRISMA flowchart of the included studies. No health technology assessments were identified for inclusion. Two non-randomized studies^{15,16} were identified regarding different procedural access points for TAVI. These studies were excluded because they did not meet the inclusion criteria for study design, but are summarized in Appendix 2.

Summary of Study Characteristics

The NICE report “Interventional procedure overview of transcatheter aortic valve implantation for aortic stenosis” was published in 2001.¹⁰ The literature search was updated to April 2011, and included two RCTs (PARTNER 1 and PARTNER 2),^{11,12} one systematic review,¹⁷ one non-randomized comparative study,¹⁸ four case series,¹⁹⁻²² and one unpublished case series, covering a total of 5,961 patients. Studies’ characteristics, with key efficacy and safety findings, as well as limitations of separate studies were listed in details in the NICE report overview. *Efficacy outcomes* included technical success of TAVI, haemodynamic and symptomatic improvements as compared to SAVR, survival rate, and quality of life. *Safety outcomes* included 30-day mortality, cerebral complications, tamponade and ventricular perforations, aortic rupture, aortic regurgitation, valve-in-valve surgery, coronary obstruction and myocardial infarction, endocarditis, arrhythmia and need for permanent pacemaker, renal failure, vascular complications, and other issues with the device. The systematic review¹⁷ included in the NICE report mainly included case series and case reports. The majority of the included case series followed patients for 30 days. The two RCTs^{11,12} compared TAVI to standard care¹¹ and TAVI to surgical valve replacement¹². Patients were followed for a median time of 2.8 years¹¹ and 1.4 years¹².

The included guidelines were published in 2008¹³ and 2011¹⁴ in the UK and South Africa, respectively. The guidelines were issued by NICE¹³ and by the South African Heart Association¹⁴ together with two of its special interest groups: South African Society of Cardiovascular Intervention and the Society of Cardiothoracic Surgeons of South Africa. The NICE guideline¹³ provides recommendations for the appropriate patient population for TAVI. The guideline also outlines the TAVI procedure and various approaches. The South African Heart Association guidelines¹⁴ provide recommendations for the requirements and structure of the multidisciplinary team performing TAVI, patient selection, and the establishment of a TAVI program.

The characteristics of the included systematic review and the included randomized controlled trials are summarized in Table 2 and 3 respectively.

Table 2: Characteristics of Included Systematic Review

First Author, Publication Year, Country	Literature Search Strategy	Inclusion Criteria	Exclusion Criteria
NICE ¹⁰ , 2011, UK	MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases searched to 11 November 2010 and updated to 19 April 2011. Trial registries and the Internet were searched. No language restriction.	Clinical studies Patient population: Patients with aortic stenosis Intervention: Transcatheter aortic valve implantation Outcomes: Safety and/or efficacy data	Abstracts with no clinical outcomes reported, reviews, editorials, laboratory or animals studies, conference abstracts, non-English language articles

Table 3: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator (s)	Clinical Outcomes
Leon ¹¹ , 2010, USA (Partner 1)	Multi-centre, active-treatment controlled RCT Duration: 1.6 years (median)	n=358 patients with severe aortic stenosis considered not suitable for conventional surgery	TAVI under general anaesthesia (transfemoral route)	Standard treatment (including balloon aortic valvuloplasty in some patients)	Death (any cause), death from CV causes, NYHA functional class, repeat hospitalization because of valve- or procedure-related clinical deterioration, MI, stroke, acute kidney injury, vascular complications, bleeding, 6-minute walk distance, and valve performance
Smith ¹² , 2011, USA (Partner 2)	Multi-centre, active-	n=699 patients with severe aortic stenosis and	TAVI under general anaesthesia	Surgical Aortic-Valve Replacement	Death (any cause), death from CV causes,

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator (s)	Clinical Outcomes
	treatment controlled RCT Duration: 1.4 years (median)	cardiac symptoms (NYHA class I function or worse). All patients were considered to be high risk but still suitable for conventional surgical aortic valve repair.	(transfemoral or transapical route)		NYHA functional class, repeat hospitalization because of valve- or procedure-related clinical deterioration, MI, stroke, acute kidney injury, vascular complications, bleeding, 6-minute walk distance, and valve performance

CV=cardiovascular MI=myocardial infarction NYHA=New York Heart Association
 RCT=randomized controlled trial TAVI=transcatheter aortic-valve implantation

Summary of Critical Appraisal

The systematic review¹⁰ was generally well conducted. A comprehensive literature search was performed following the establishment of a research question and inclusion criteria. The characteristics of included and excluded studies were provided in detail and the scientific quality of included studies was assessed. It was unclear whether there was duplicate study selection and data extraction. Although the conflict of interest was documented for each of the included studies, the systematic review did not include this information.

The two RCTs^{11,12} were also generally well conducted. The objective, main outcomes and main findings were clearly described. The standard therapy was not described in detail in one of the randomized controlled trials.¹¹ Both RCTs blinded the individuals measuring the main study outcomes, but did not blind the study subjects to the intervention that they received. Both RCTs performed appropriate statistical tests to assess the main outcomes. Though both RCTs used an adequate method of randomization, it was unclear whether the randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete.

The guidelines' scope, purpose, and recommendations were clear.^{13,14} Individuals from relevant professional groups were involved in developing both guidelines. It was unclear in both of the guidelines whether patients' views and preferences were sought and whether the guidelines had been piloted among target users. It was unclear whether the South African guideline¹⁴ used systematic methods to search for evidence. It was also unclear what methods the British guideline¹³ used for formulating the recommendations.

A complete summary of the critical appraisal of the included studies and guidelines can be found in Appendix 3.

Summary of Findings

Evidence for each research question is presented separately.

1. What is the clinical effectiveness (including documented mortality reduction) of transcatheter aortic valve implantation in adult patients with aortic stenosis who are ineligible for cardiac surgery?

The summary below lists main efficacy findings from the NICE systematic review,¹⁰ with focus on the findings from the two RCTs. It is noteworthy that the RCT by Leon *et al.* (PARTNER 1)¹¹ compared TAVI to standard therapy (which includes balloon-aortic valvuloplasty), while the RCT by Smith *et al.* (PARTNER 2)¹² compared TAVI to SAVR.

Technical success

Short term procedural success (defined as valve deployment, retrieval of delivery catheter, no conversion to conventional surgery and patient leaving interventional room alive) was observed in the majority of TAVI patients (94%).¹⁰

Haemodynamic improvement

Greater haemodynamic improvement was reported.¹⁰ Statistically significant higher mean aortic valve area (1.59 cm² versus 1.44 cm², P = 0.002) and lower mean aortic valve gradient (10.2 mmHg versus 11.5 mmHg, P = 0.008) were observed in the TAVI group compared to the SAVR group.¹² There was also a significant increase in left ventricular ejection fraction at 30 days compared with baseline in the TAVI group (from 54% at baseline to 58% at 30 days, P < 0.001).¹¹

Symptomatic improvement

75% of the TAVI group were asymptomatic or had mild symptoms, compared to 42% in the standard therapy group; the difference was statistically significant (P < 0.001).¹¹

Survival (beyond 30 days)

There were fewer deaths observed in the TAVI group at 1 year compared with the standard therapy group (31% versus 51%); the difference was statistically significant (P < 0.001).¹¹

Quality of life

In a case series of 99 TAVI patients, there was a statistically significant improvement in summary physical health score from baseline to 3-month follow-up. There was also an improvement in summary mental health score after 3 months, but the difference did not reach statistical significance.²¹

2. What is the clinical evidence regarding different possible procedural access points for transcatheter aortic valve implantation?

The literature search did not identify any systematic reviews or RCTs that showed the clinical evidence for different procedural access points for TAVI. Data from two excluded non-randomized studies^{15,16} showed that minimum femoral dimension needs to suit the size of access sheaths and catheters for the CoreValve device and for the Edwards Sapien device. Recently, femoral access risk ratio, defined as sheath size (Fr)/femoral artery diameter, was shown to be an independent predictor of major vascular complications. Details on these non-randomized studies are summarized in Appendix 2.

3. What is the clinical evidence regarding long-term success and complication rates associated with transcatheter aortic valve implantation?

The summary below lists the main complication rate findings from the NICE report, with a focus on the findings from the two RCTs (PARTNER trials).

30 day mortality

Similar rates of mortality (cardiovascular cause) (3%) within 30 days were found in the TAVI group and the SAVR group.¹² In the PARTNER 1 trial, the mortality (cardiovascular cause) rate was 5% in the TAVI group compared to 2% in the standard therapy group; the difference was not statistically significant.¹¹

Cerebral complications

A higher rate of stroke or transient ischemic attack was reported at one year in the TAVI group (8%) compared to the SAVR group (4%); the difference was statistically significant. The rates were also higher in the TAVI group compared to the standard treatment group (7% versus 2%); the difference was statistically significant (P = 0.03).

Aortic regurgitation

Aortic regurgitation was observed in 15% of patients treated with TAVI after one year compared to 17% of those treated with standard therapy (P-value not reported).¹¹

Arrhythmias and need for permanent pacemaker

Similar proportions of patients with TAVI and with SAVR required a new pacemaker within one year (6% versus 5%); the difference was not statistically significant.¹² Within 30 days, the need for a new pacemaker was reported in 3% of patients treated with TAVI compared to 5% in those treated with standard treatment (P-value not reported).¹¹

Vascular complications

There was a higher proportion of patients with major vascular complications within one year in patients with TAVI compared to those with SAVR (18% versus 5%); the difference was statistically significant (P < 0.001).¹² Within 30 days, more patients treated with TAVI reported vascular complications and major bleeding than those treated with standard treatment (31% versus 5%); the difference was statistically significant (P = 0.007).¹¹

4. What are the evidence-based guidelines and criteria regarding selection of optimal candidates for transcatheter aortic valve implantation?

Optimal patient selection is vital to a successful TAVI procedure. NICE Guidance for TAVI¹³ stated:

- “The evidence on TAVI is limited to small number of patients who were considered to be at high risk for conventional surgery.”
- “Clinicians should ensure that patients understand the uncertainty about the long-term efficacy and risks of the procedure.”
- “Patient selection should be carried out by a multidisciplinary team including interventional cardiologists, a cardiac surgeon and a cardiac anaesthetist.” (Section 1: Guidance)

The Joint Consensus Statement and Guideline on TAVI by the South African Society of Cardiovascular Intervention¹⁴ stated:

- “The performance of TAVI should be restricted to a limited number of high-volume centres which have both cardiology and cardiac surgery departments.”
- “TAVI should be reserved for patients who, after evaluation by a multidisciplinary team, are found to have a risk/benefit ratio favouring TAVI rather than conventional surgery.”
- “TAVI should be contra-indicated for significant other valve lesions or coronary artery disease that require coronary bypass surgery, and in patients whose life expectancy is expected to be less than one year.” (Sections 1 and 3, Consensus Guidelines on TAVI)

Limitations

One systematic review was identified, based mainly lower quality evidence. There were only two randomized controlled trials comparing the performance of TAVI to standard therapy or conventional surgical aortic valve repair identified. More randomized studies with large populations and long-term follow up are needed. Though the two randomized controlled trials were generally well conducted, one RCT¹¹ did not describe the comparator or standard therapy. The levels of evidence and the strength of the recommendation were not graded in the guidelines, leaving uncertainty with regards to the reliability of the evidence that the recommendation was based on and the strength of each recommendation.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

TAVI represents a viable alternative for patients with severe aortic valve stenosis who are not eligible to standard surgery treatment, with statistically significant clinical benefits. However, long-term success and complication rates of the procedure are uncertain at the present time. No evidence that met the study inclusion criteria regarding procedural access points was identified. Existing guidelines and reviews suggested that strict patient selection and procedural considerations following consultation with a multidisciplinary team are vital to the success of TAVI.

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439

www.cadth.ca

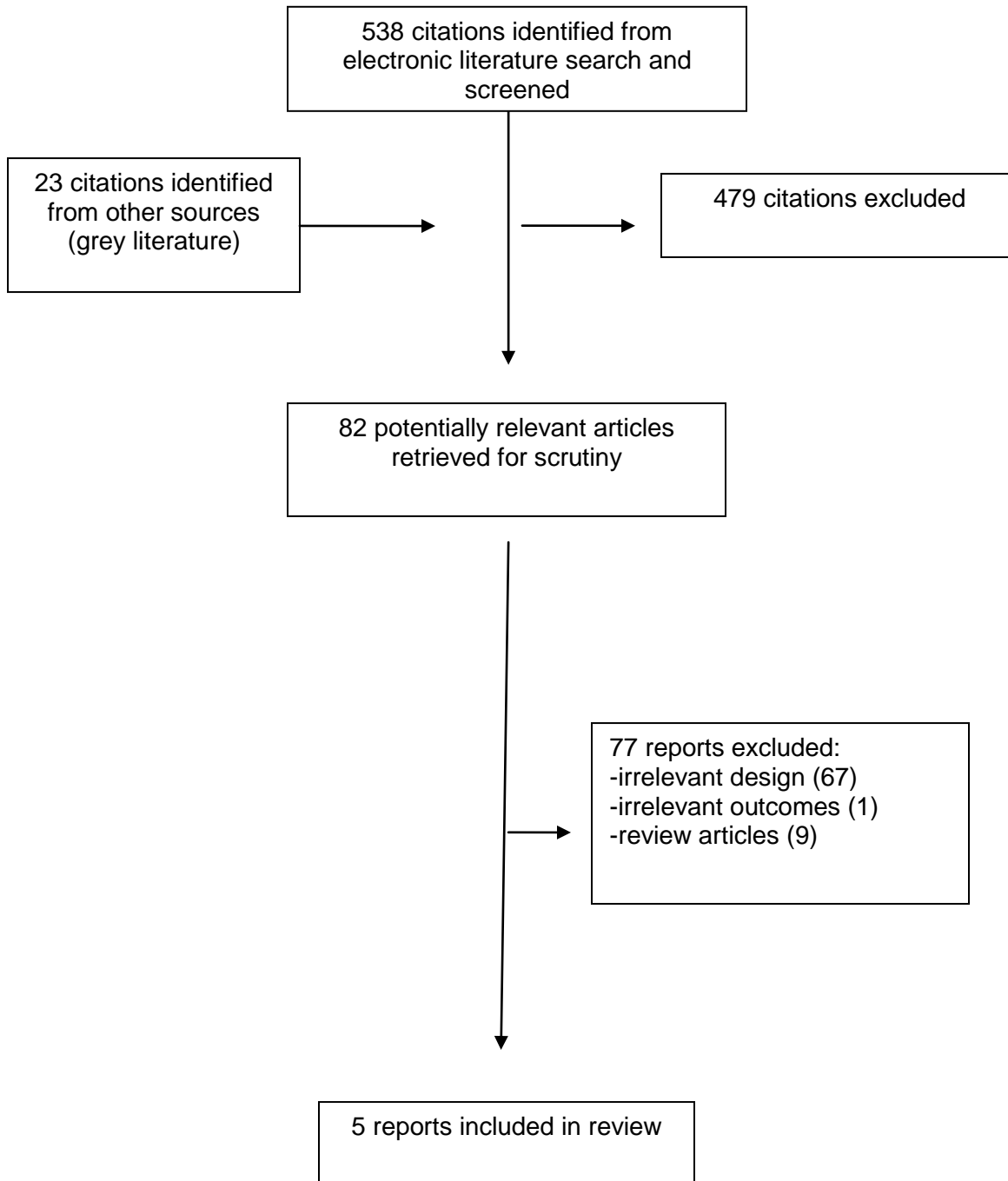
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APPENDICES:

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Details of Excluded Non-randomized Studies on Procedural Access Points

First Author, Publication Year, Country, Study Type	Study Population	Intervention	Results, Author Conclusions
Hayashida ¹⁶ , 2010, France, Conference Abstract; NRS	85 transfemoral TAVI patients	Percutaneous femoral artery closure	The femoral access risk ratio which is defined as sheath size/minimal femoral artery diameter was the only predictor of femoral perforation and access site complications. This new criterion could help patient selection for the percutaneous approach.
Jilaihawi ¹⁵ , 2010, UK, NRS	100 patients with aortic stenosis at high risk for conventional surgery	Transthoracic or transesophageal echocardiography and invasive angiography to assess the anatomical suitability of each TAVI approach.	Edwards suitability was 28% for Edwards Sapien transfemoral, 78% for Edwards Novaflex transfemoral, and 88% for Edwards-Sapien transapical. MC suitability was 84% for transfemoral and 89% using additional transaxillary and direct aortic approaches. Only 3% of patients were anatomically unsuitable for all approaches.

MC=Medtronic CoreValve NRS=non-randomized study TAVI=transcatheter aortic valve implantation

APPENDIX 3: Summary of Critical Appraisal of Included Studies

First Author, Publication Year	Strengths	Limitations
Systematic Reviews		
NICE ¹⁰ , 2011	<ul style="list-style-type: none"> • Comprehensive literature search performed based on pre-defined criteria • Characteristics of included and excluded studies provided • Scientific quality of the included studies was assessed, documented, and included in the conclusions 	<ul style="list-style-type: none"> • Unclear whether there was duplicate study selection and data extraction • An assessment of publication bias was not undertaken • Conflict of interest was not stated
Randomized Controlled Trials		
Leon ¹¹ , 2010 (Partner 1)	<ul style="list-style-type: none"> • Baseline characteristics of patients equally distributed between groups • Individuals measuring the outcomes were blinded • Adequate method of randomization • Adequate adjustment for confounding in the analysis • Power calculation performed to determine adequate sample size 	<ul style="list-style-type: none"> • Standard therapy not described • Study subjects were not blinded to the intervention that they received • Unclear whether the randomized intervention assignment was concealed from both patients and health care staff • Characteristics of patients lost to follow-up were not described
Smith ¹² , 2011 (Partner 2)	<ul style="list-style-type: none"> • Baseline characteristics of patients equally distributed between groups • Individuals measuring the outcomes were blinded • Adequate method of randomization • Adequate adjustment for confounding in the analysis • Power calculation performed to determine adequate sample size 	<ul style="list-style-type: none"> • Study subjects were not blinded to the intervention that they received • Unclear whether the randomized intervention assignment was concealed from both patients and health care staff • Characteristics of patients lost to follow-up were not described
Guidelines		
NICE ¹³ , 2008	<ul style="list-style-type: none"> • Scope and purpose of the guidelines are clear • The recommendations are specific and unambiguous • The method for searching for and selecting the evidence are clear • Health benefits, side effects and risks were stated in the recommendations • Target users of the guideline are clearly defined 	<ul style="list-style-type: none"> • Unclear whether the guideline was piloted among target users • It was unclear whether patients' views and preferences were sought • Methods used for formulating the recommendations are not clearly described • Procedure for updating the guidelines is not provided • Potential cost implications of applying the recommendation are not included in the recommendation
SASCI ¹⁴ , 2011	<ul style="list-style-type: none"> • Scope and purpose of the guidelines are clear • The recommendations are specific and unambiguous • Target patient population is clear • References are provided to support each recommendation • Guideline development group includes individuals from all the relevant professional groups 	<ul style="list-style-type: none"> • It was unclear whether patients' views and preferences were sought • The method for searching for and selecting the evidence was unclear • Unclear whether the guideline was reviewed externally prior to publishing • Health benefits, side effects and risks not explicitly stated in the recommendations