This item is the archived peer-reviewed author-version of:

What are the main predictors of in-hospital mortality in patients with infective endocarditis : a review

Reference:

Mistiaen Wilhelm.- What are the main predictors of in-hospital mortality in patients with infective endocarditis : a review
Scandinavian cardiovascular journal - ISSN 1401-7431 - Abingdon, Taylor & Francis Ltd, 52:2(2018), p. 58-68
Full text (Publisher's DOI): <https://doi.org/10.1080/14017431.2018.1433318>
To cite this reference: <https://hdl.handle.net/10067/1482200151162165141>

Predictors of in-hospital mortality in patients with infective endocarditis: a review

Running title: Mortality in endocarditis

Wilhelm P Mistiaen

University of Antwerp, Faculty of Medicine & Health Sciences, Department of Rehabilitation Sciences and Physiotherapy Antwerp, Belgium

Artesis-Plantijn University College of Antwerp, Dept. of Healthcare & Wellbeing

Address for correspondence

Wilhelm P Mistiaen MD, ScD, PhD

University of Antwerp

CDE,

Universiteitsplein 1

2610 Antwerp

Belgium

wilhelm.mistiaen@uantwerpen.be; wilhelm.mistiaen@ap.be

presented as abstract 60292 at Heart Failure 2017 and the 4th World Congress on Acute Heart Failure

Abstract

Background

Infective endocarditis (IE) is a serious condition with a high 30-day mortality. Surgery is needed in many patients. The preoperative hemodynamic status (congestive heart failure, need for urgent/emergent surgery, need for mechanical support, NYHA functional class III/IV) could have an impact on postoperative outcome. Each of these parameters is an indication for the inadequacy of the left ventricle to maintain an adequate circulation

Evidence acquisition

A literature search was performed using “endocarditis AND hospital mortality OR outcome AND predictor” and “International Collaboration on Endocarditis – Prospective Cohort Study” in Web of Science database, from 2010 to 2017. The focus was hospital mortality and its predictors. Manuscripts were excluded if no logistic regression or propensity analysis was available in the analysis. The predictors were ranked according the odds ratios.

Evidence synthesis

Most studies are coming from one tertiary center and are retrospective, with different designs. Recruitment periods are long and sample sizes small. Definitions of preoperative events such as hemodynamic status are not uniform. Thirty-day mortality varies between 10 and 50%. In 7 of 14 papers where the hemodynamic status is included, it is ranked as first and in 3 as second, with highest odds ratio

Conclusions

The heterogeneity of the included papers, lack of uniform definitions of preoperative events, small sample sizes and long inclusion periods precludes a proper meta-analysis. Nevertheless, heart failure and a compromised hemodynamic status can be identified as the dominant predictor for 30-day mortality of IE. This seems avoidable by early surgery.

Introduction

The incidence of infective endocarditis (IE) is estimated between 3 and 10 cases per 100,000 person-years. This incidence is not decreasing over time (1-6). IE is a heterogeneous disease which affects several organs (7) and has therefore a wide difference in mortality (8). Complications such as congestive heart failure (CHF), stroke or other events contribute to its morbidity (1,9-11). In 10 to 30% of the cases, a prosthetic valve is affected. Prosthetic valve endocarditis (PVE) has a more severe course (12), with more perivalvular extension (13) and more staphylococci involved (14). PVE occurs in 1 to 6% after first 5 year of implantation (15-18). Thirty-day mortality of IE is high but is improving from 30-40% to 15-20% (5,6,10,11,19-21). This might be due to the increase of *S. aureus* as infective agent (5,22), which has a higher mortality of 40-80% (19,23), especially in cases of PVE.

Surgery is one of the modes of treatment of IE. Its mortality is high (up to 36%) but decreasing (24, 20). Surgery can improve survival of IE (25). According to existing guidelines, surgery is needed in case of CHF, uncontrollable infection, high risk for embolism and intra-cardiac damage (12,15,20, 25-27). Surgery could be needed in the acute phase of IE in 60-70% of the patients (1,24). Others state that surgery is needed in 25-30% in acute phase and in 20-40% at a later stage (20,25). Surgery also seems best option in prosthetic valve endocarditis or PVE (13), but with indications which might be different compared to native valve endocarditis or NVE (28).

The main research question is: what is the dominant modifiable predictor for early (or 30-day or hospital) mortality of IE. This could help to identify which patient will benefit most from surgery. Secondary questions are: in which degree are the series heterogeneous in terms of study design, baseline variables and definitions. What are the definitions of surgical parameters of “acute phase”, “early”, “urgent” and “emergent”. What are the potential dilemmas, biases and limitations which have been encountered?

Methods

A literature search was performed with the search terms “surgical aortic valve replacement AND hospital mortality AND predictor* AND endocarditis” and with “surgical aortic valve replacement AND outcome AND predictor* AND endocarditis” in Web of Science database, from 2010 to 2016. There were 24 and 35 hits with 9 double references. Using the search terms “International Collaboration on Endocarditis – Prospective Cohort Study” resulted 26 more articles but only 5 more were included. There were 5 double manuscripts, 5 abstracts, 1 non-English, and 1 concerning cardiac devices. The remaining manuscripts did not include hospital mortality as outcome or had no logistic regression. Manuscripts were included if infective endocarditis according to the Duke University diagnostic criteria (29), either native valve endocarditis (NVE) or prosthetic valve endocarditis (PVE) or both were considered for surgical treatment. Manuscripts were excluded if no logistic regression was available or if hospital or 30-day mortality was not included. This resulted in 30 included manuscripts. Articles published before 2010 are mentioned if relevant, but not included in the analysis.

Results

Most series are descriptive (1,5,7,10,19,21,24,-26,30) in which the authors do not pose specific research questions. Almost all centers have included only patients with IE. In two surgical series the outcome of patients with and without IE are compared (16,24). Seventeen series consist of solely surgical patients (table 1). In other series, medical and surgical outcome is compared in PVE patients (30) or the focus is directed towards the effect of

preoperative treatment in PVE on postoperative outcome (12,13). Only one RCT could be found, which has severe patient inclusion restrictions due to ethical constraints (27). Two manuscripts handle nationwide data (6,31). Eight papers have a focus on timing of surgery (26,28,32), with respect to delay in diagnosis (12), in patients with NVE (15) or with PVE (33) or when *S. aureus* is involved (23) or after stroke (9). Although the focus is often directed on the need for surgery, surgical indications are described explicitly in only eight manuscripts. These include CHF, presence of large vegetation, recurrent emboli, prosthetic valve dysfunction, severe valve regurgitation, sepsis, abscess (1,12,13,17,25,26,32,34). Contraindications such as hemorrhagic stroke are stated explicitly in only one manuscript (25). One dilemma is the prevention of stroke by early surgery (27,32) versus the inherent risk of operating during active infection. Timing of surgery is even more controversial in patients with stroke (9). At best, timing for surgery in these cases depends on expert opinion (17).

Some papers have a specific design. These include 1) a historic comparison of treatment modalities in two different eras (10,26), 2) the effect of referral bias and eligibility for transfer (35), 3) the effect of gender on the decision making (36) 4), microbial issues (20) or antibiotic regimen (4,37) and 5) the effect of “imposed medical treatment”, i. e. contraindication for surgery (3). Attempts are made to identify high risk patients by a scoring system (3,22,25).

In and exclusion criteria vary considerably. Inclusion criteria of patients are likely or definitive diagnosis of IE according to the Duke criteria. Some papers have additional criteria because of their focus on subgroups of patients, such as reoperative surgery in elderly (16,38,39), *S. aureus* in patients with PVE (23), with neurological complications of IE (10), with CHF (11) or mild renal dysfunction (19), with multivalve involvement (2), or with aortic root involvement. For the latter group, the use of homograft and other types of aortic root replacement is studied (13,17,34,40). Exclusion criteria in some papers are hemorrhagic stroke (9,27), NVE (23,33), right sided IE (10,23,34), intravenous drug users (23), pacemaker-IE (10, 15, 33), CHF, AV-block or abscess (2,27,34), PVE (2,15,27) and hemodialysis (19). In the only available RCT, stringent exclusion criteria had to be built in for ethical reasons (27).

Special techniques of statistical analysis are applied in some series in order to deal with difficult problems such as bias due to gender, survivor, selection and referral bias (35, 36, 15, 33, 5). These authors include propensity analysis (3,15,23,32,33), instrumental variable analysis (15), inverse probability of treatment weighting or IPTW (33), analysis for survivor bias (4,15,23) or for selection bias (23,33). However, application of propensity score, as a regression model, with IPWT and surgery as covariate showed conflicting results (28).

The results of the papers are summarized in the tables.

Table 1 shows that most series are single centered and of retrospective nature. One series is derived from two centers and another from 8 centers. Most series are also relatively small (nineteen series have less than two-hundred, 7 series have between 200 and 500 patients, and five have over 500 and one is nationwide). Seven papers are derived from prospectively collected ICE-PCS databases. Eighteen papers include solely surgical patients. Seven papers address only patients with PVE, five papers address only patients with NVE. The other manuscripts describe mixed populations

Table 2: Gender and age are universally included. Although several important clinical parameters are described in the text as baseline characteristic, these cannot always be found in the univariate analysis. Furthermore, some parameters have to be represented as one group for reasons of clarity and because of lack of uniform definition. This applies to hemodynamic

status “urgent” with “emergent” and “salvage” surgery. Congestive heart failure is grouped with higher NYHA functional class, need for inotropic medication or need for mechanical support. Sepsis, septic shock, persistent blood culture and persistent fever are also grouped. Increased creatinine, renal dysfunction and need for hemodialysis are also taken together. For microbial data, the main focus is usually *S. aureus* and culture negative status.

Table 3 shows the years of data collection, patient age (mostly as mean and standard deviation), the percentage of aortic involvement and the percentage of *S. aureus* as causative agent. Six papers focus entirely on the aortic valve IE and one on *S. aureus*.

Table 4 shows the rate of preoperative complications of IE. Stroke, CHF and the presence of abscess vary considerably. Only one paper deals exclusively with preoperative CHF and one with preoperative stroke. In three papers, only patients with an abscess are included. Nine papers deal exclusively with active IE. In one paper (28), a separate statistical analysis has been performed for patients with NVE and with PVE.

Table 5 shows the hospital mortality as well as its predictors. The hospital mortality varies between 6 and 33%. The identified predictors depend on the study design and the parameters included. If included, left ventricular factors (hemodynamic state, and preoperative CHF) play a dominant role. The hemodynamic status and CHF is analyzed in 14 papers. In 7 papers, these parameters are ranked first according the odds ratio (10,12,22,26,28,34,36), in 3 papers (11,16,30), it is ranked second, in one as third (1) and in 3 papers, it is only identified as a risk factor in the univariate analysis, but with a low number of fatalities, however (21,25,41). Sepsis and septic shock is analyzed in 13 papers, but is ranked first in only 3 papers (14,16,30), but mostly in patients with a perivalvular abscess. Renal failure and plasma creatinine (17,19) were identified as main predictor in two series. Other factors were only once identified as being most important. In several papers (10,26,30), there might be overfitting of the multivariate analysis and some parameters, (septic shock, severe sepsis, uncontrolled infection, WBC count), could point point to the same condition. One paper (24) was not included in the table because the logistic regression applied to all operated patients, of whom only 8% had IE.

Discussion

The interpretation of these tables is complicated by several factors. First, the variables included differs between papers: some papers focus on laboratory or microbial parameters, others on referral problems or surgical aspects. In many papers, data are missing, especially if these have been derived from larger but less detailed databases. There is also the possibility of coding errors and under or overreporting. This may confound any analysis. Second, the definition of terms is not always uniform. Hemodynamic parameters and related to this, timing of surgery seem of most importance. “Early surgery” can be defined as within one (27) or 2 weeks (32), or during index hospitalization (15,28,33). Surgery during active IE means operating under antibiotic treatment (22,25,42) or during fever, positive culture, WBC elevation, septic shock or presence of abscess (2). Timing for surgery is also related to the hemodynamic status. For this reason, mentioning of timing is superfluous in patients needing urgent or emergent surgery. Urgent surgery is mostly defined by surgery index hospitalization (16,22,26,39). Hence this definition overlaps with that of “early surgery”. In one paper urgent surgery is defined as less than 24h after admission (30). This, however, is usually labeled as emergent surgery (16,26). This term is also used if surgery is performed without delay (22) or in unstable patients (39). The term “salvage” is coined only once (26) and refers to an immediate intervention in order to save the life of the patient. Third, some studies are devoted

to valve replacement in general, with attention to the effect of IE on postoperative outcome, and not solely to patients with IE (16,24). Fourth, surgical centers are not always comparable. In one series for example, IE accounts for 8% of the operations with a mortality of 17% in patients with IE and 9% in patients without IE. This figure is high considering that the mean age of the latter group is 52 years (24). In a comparable design, mortality was 6.8% in a patient group with a mean age of 58 years, undergoing a more hazardous reoperation (16). Fifth, preoperative conditions can have varying definitions. These include CHF, renal dysfunction and neurological complications. CHF can be assessed according symptoms and signs (30), by radiological signs (11), by functional NYHA class (23), unstable hemodynamics (39), or according Framingham (10) and AHA guidelines (3). Definitions of preoperative renal dysfunction include $>133\mu\text{mol/L}$ (30), $>200\mu\text{mol/L}$ (16,17), $>2\text{mg\%}$ (2,22,26,43), estimated GFR $<60\text{ml/min}$ (19, 25), need for hemodialysis (11) or is mentioned without definition (3,12,13,21,23). A distinction between chronic and acute renal dysfunction is not made. Definitions of neurological complications are also not uniform. Ischemic stroke is most commonly mentioned, but sometimes non-focal neurological signs and symptoms are also involved (3,15,30). Ischemic cerebral events might be classified as clinically silent or minor versus moderate-to-severe (10,25). Even with CT, some remain undetected. Some more definitions are not uniform: the early type of PVE is mostly defined as occurring within the first postoperative year (10,12,16,17), one author used 60 days as cut-off $<60\text{d}$ (23). Interpretation of the results are also hampered by the inhomogeneity of IE (13,21,24,41), absence of input in treatment before referral (13,21), and in some surgical series, the absence of medical cohort (12,16,26). A number of biases has also been identified. These include selection bias (3,11,22,27,20,25,27,30,32,34-37), referral bias because of voluntary participation by tertiary centers (4,9,15,19,23,33), treatment bias (14,30) and survivor bias, which can be defined as patients living longer are more likely to undergo surgery (15,28,30). To alleviate for these limitations, statistical techniques such as a propensity analysis and adjustment for survivor and treatment bias are performed (15,33). Other limitations include a small sample size and hence a relatively low number of adverse events. Some effects, therefore might remain undetected. A lengthy inclusion time could imply a learning curve and a considerable improvement of practice over the years, which makes comparison of patients within one series difficult. Last but not least, most data are derived from a single center, the results are not necessary generally applicable.

Infective endocarditis is becoming an increasingly difficult entity to treat because of cardiac valve implants (31), increased patient age, increased contact with healthcare facilities with healthcare-related IE (37) and *S. aureus* as infective agent (15). The mortality of IE is high in case of aortic involvement (1), in case of PVE (16,30), if complicated by an abscess (14,17,30), a moderate-to-severe ischemic stroke (10,25) and hemorrhage (10). Surgery for IE is often needed (30) and lowers mortality (11,23) but it remains challenging (22). In patients with PVE, the benefit is less clear compared to NVE (15,33). The mainstay is a radical excision of all infected tissue (21) with valve replacement or repair if possible (7,22,41). The techniques have become more extensive (26). The choice of the valve seems of lesser importance (21) and in case of aortic root replacement, homografts (13,34,40) as well as Bentall/Cabrol techniques have been applied successfully (17). In case of mitral involvement, repair is preferable over replacement (7). Early surgery improves outcome in IE (11,20) and especially in NVE (28,32) with presence of large vegetation (10) and other complications. It decreases the risk for embolism (27). However, an operation in active phase is related to LCOS (1) and high mortality (13). Hence, timing of surgery is still a controversial issue (28, 33, 25) and especially for PVE, this needs further evaluation (28,33), since the mortality remains high (16,17,30). The optimal timing for surgery is also difficult in patients with ischemic stroke, but in presence of indications, there should be no delay (9), because of its

protective effect (3,15,28,33,36). A team decision should avoid delay (7,21), and many advocate individualized decisions (7,23). When surgery is contraindicated, the prognosis is dismal (3,5). In such patients, all options must be carefully considered.

Conclusions

Many authors consider their approach as reasonable with good reason, but the limitations identified within the papers are inherent to the methodology. The next best option for an RCT is a multicenter prospective registration of patients such as in the International Collaboration on Endocarditis – Prospective Cohort Study. In such registration, a common ground has to be found on which parameters to include. For a heterogeneous disease as IE, a proper choice is difficult. However, risk factors identified in the included series deserve consideration in this respect. This applies especially for the hemodynamic status, renal dysfunction, neurologic complication and paravalvular extension. It is also of utmost importance to agree on common definitions of “emergent” and “urgent” surgery, “early surgery”, “early PVE”, renal dysfunction. In spite of all inhomogeneities, biases and limitations, a major pattern can be distinguished from the tables. In 14 papers, left ventricular factors (hemodynamic status and CHF), were included in the statistical analysis. In 7 of these manuscripts, these factors were identified as the most clinically relevant predictor for mortality. This indicates that a heterogeneous disease as IE, with widely different circumstances an impaired hemodynamic status and CHF points to a need for operation before the condition of the patient and hence the short-term outcome worsens.

Limitations

Infective endocarditis is a heterogeneous disease. The papers included also are very different in patient population and design. Sometimes, the papers are purely descriptive, sometimes they focus on referral policy or on specific subgroups. Definitions of major preoperative condition such as heart failure, renal dysfunction, stroke and need for urgent or emergent surgery differ considerably. Moreover, many biases have been identified by the authors. Last but not least, in some series, all patients are operated, but other included also non-operated patients for various reasons. This makes comparison of the included papers very difficult. In spite of the differences between the papers, there are several important messages: first, registration and definitions need to be agreed on and second, preoperative decrease in left ventricular function (in all its various definitions) is an ominous sign.

Conflicts of interest: none to declare

Acknowledgements: none to declare

Funding: none to declare

Table 1: design of the included papers

Author	n	centers	%NVE	%PVE	% surgery
Adademir 2014	174	single	84.5	15.5	100
Alonso-Valle 2010	122	single	0	100	21.3**
Barsic 2013	198	ICE-PCS	72.5	23.0	100
Caes 2014	186	single	82.0	18.0	100
Carugati 2013	178	ICE-PCS	81.3	18.7	50.8
Chirouze 2015	168	ICE-PCS	0	100	100
Dunne 2014	85	single	89.5	10.5	100
Funakoshi 2011	212	single	100	0	81.1
Gaca 2011	19,543	NW	79.4	20.6	100
Garcia 2013	1345	8 centers	76	24	39
Grubitzsch 2014	149	single	0	100	100
Kang 2012	76	single	100	0	88.6
Kiefer 2011	1359	ICE-PCS	78.1	21.9	61.7
Koeda 2013	119	single	88	12	76
Korem 2014	70	single	52.8	25.7	15.7
Lalani 2010	1552	ICE-PCS	100	0	46
Lalani 2013	1025	ICE-PCS	0	100	47.9
Leontyev 2011*	152*	single	0	100	100
Leontyev 2012	172	single	55.8	44.2	100
Machado 2014	64	single	53	47	100
Marks 2015	336	single	79.2	20.8	99
Musci 2010	349	single	0	100	100
Musci 2010b	1163	single	73.5	26.5	100
Ohara 2012	447	NW	80.0	19.9	26.2
Ota 2011	152	single	100	0	100
Pang 2015	191	single	92.7	7.3	100
Perrotta 2010	62	single	50	50	100
Rasmussen 2011	323	two centers	100	0	60
Rouzé 2016	207	single	67	33	100
Sambola 2010	271	single	-	-	41
Spiliopoulos 2014	94	single	90.3	9.7	100
Thuny 2012	332	single	72	28	57
Wilbring 2012	31	single	0	100	100

* comparison of redo-AVR for PVE (n=152) v. other indications (n=161)

** there were 133 periods of infective endocarditis

ICE-PCS: international collaboration on endocarditis – prospective cohort study; n: number; NVE: native valve endocarditis; NW: nation-wide; PVE: prosthetic valve endocarditis.

Table 2: parameters under study within the included papers

Author	HS	CHF	RD	AB	S	CNS	MB	OSP	N/P	ST
Adademir 2014	+	+	+	+	+	+	+	+	+	-
Alonso-Valle 2010	+	+	+	+	+	+	+	-	NA	-
Barsic 2013	-	+	+	+	+	+	+	-	+	+
Caes 2014	+	+	+	-	-	+	+	+	+	NA
Carugati 2013	-	+	+	+	+	+	+	-	+	-
Chirouze 2015	-	+	+	+	-	+	NA	-	NA	+
Dunne 2014	-	+	-	-	+	+	+	-	+	+
Funakoshi 2011	-	+	+	+	+	+	+	-	NA	+
Gaca 2011	+	+	+	-	+	-	-	+	+	-
Garcia 2013	-	-	-	-	-	NA	+	-	+	-
Grubitzsch 2014	+	+	+	-	+	-	-	+	NA	NA
Kang 2012	-	NA	+	NA	NA	+	+	NA	NA	+
Kiefer 2011	-	+	+	+	-	+	+	-	-	-
Koeda 2013	-	+	+	-	-	-	+	-	-	-
Korem 2014	-	+	+	-	-	+	+	-	-	-
Lalani 2010	-	+	-	+	+	+	+	-	NA	-
Lalani 2013	-	+	-	+	-	+	+	-	NA	-
Leontyev 2011	+	+	+	-	+	+	+	+	NA	-
Leontyev 2012	+	+	+	-	-	+	+	+	NA	-
Machado 2014	-	-	+	-	-	-	-	-	-	-
Marks 2015	-	-	+	-	-	-	+	-	-	-
Musci 2010	+	+	+	+	+	+	+	-	+	-
Musci 2010b	+	+	+	+	+	+	+	+	NA	-
Ohara 2012	-	+	+	-	-	+	+	-	+	+
Ota 2011	-	+	+	-	+	+	+	+	NA	-
Pang 2015	+	+	+	+	-	+	+	+	-	-
Perrotta 2010	-	-	+	NA	-	+	+	+	+	-
Rasmussen 2011	-	+	+	+	-	+	-	-	NA	-
Rouzé 2016	+	+	+	NA	-	-	+	+	+	-
Sambola 2010	-	+	+	+	-	+	+	-	NA	-
Spiliopoulos 2014	+	+	+	+	-	+	+	+	-	-
Thuny 2012	-	+	+	NA	NA	+	+	-	+	+
Wilbring 2012	-	-	+	NA	-	-	+	NA	NA	-

+: included in multivariate analysis; - not included in multivariate analysis. NA: not applicable because of study design and selection criteria;

AB: abscess/paravalvular involvement; CHF: congestive heart failure, CNS: central nervous system complication; HS: hemodynamic status; MB: microbial (mostly focused on *S. aureus*); N/P: native or prosthetic infective endocarditis; OSP: other surgical procedures such as CABG; RD: renal dysfunction; S: sepsis / septic shock / operation during active phase; ST: surgical timing

Table 3: era of inclusion, patient characteristics

Author	era	age	% aortic	% <i>S. aureus</i>
Adademir 2014	1985-2011	39,3+/-14.4	100	13.2
Alonso-Valle 2010	1986-2005	59 (56-62)	45	13.0
Barsic 2013	2000-2006	53/55	46.5	37.0
Caes 2014	1999-2012	57.8+/-15.3	45	25.0
Carugati 2013	2008-2010	58-72	-	48.3
Chirouze 2015	2000-2006	59/64	-	100
Dunne 2014	2000-2009	50.5	37.5	54.1
Funakoshi 2011	1990-2009	54+/-17	40.1	18.4
Gaca 2011	2002-2008	55(45-66)	35.7	-
Garcia 2013	1984-2009	61	47	20
Grubitzsch 2014	2000-2010	63.5+/-13.9	61.7	11
Kang 2012	2006-2011	45.5+/-14.9	40.8	10.5
Kiefer 2011	2000-2006	59 (47-73)	44.9	28.0
Koeda 2013	1997-2011	58+/-17	39	22
Korem 2014	2009-2011	64.7+/-15.1	27.1	33.3
Lalani 2010	2000-2005	53	54.2	20.2
Lalani 2013	2000-2005	59.4	71.0	22.3
Leontyev 2011	1994-2008	65.8+/-14.7	100	27.6
Leontyev 2012	1996-2009	62+/-13	100	25.4
Machado 2014	2003-2010	64	52	52
Marks 2015	1998-2010	52 (41-67)	56.0	34.5
Musci 2010	1986-2008	59.2+/-14.9	61.6	35.2
Musci 2010b	1986-2007	55 (2-81)	100	19.2
				22.1
Ohara 2012	2006-2009	58+/-17	36	15
				28
Ota 2011	1996-2007	47 +/- 17	-	9.4
		51+/-16	-	11.4
Pang 2015	2000-2012	47.4+/-14.9	34.6	15.7
Rasmussen 2011	2002-2008	62	42.1	23.2
Rouzé 2016	1979-2014	59.9+/-15.4	100	34
Sambola 2010	2000-2008	57+/-18	41	27
Spiliopoulos 2014	1997-2007	58.3+/-13.1	58.0	17.0
Thuny 2012	2002-2008	61+/-16	57	24
Wilbring 2012	2007-2010	57.5+/-2.6	100	32

Age: as mean +/- standard deviation or as median with range

Musci 2010b; Ohara 2012: figures given separately for native and for prosthetic valve endocarditis; Ota 2011: figures separately given for single and multivalve endocarditis

Table 4: preoperative complications of infective endocarditis: expressed as %

Author	CHF	stroke	abscess	urg/emerg	active IE
Adademir 2013	55.7	8.0	24.1	- /14.9	48.3
Alonso-Valle 2010	-	-	-	38.3 / -	-
Barsic 2013	45	100	30.5	-	9
Caes 2014	-	47/186	23.5	80.0/14.0	100
Carugati 2013	35.8	23.8	40.0	-	23.8
Chirouze 201	28/23	33/37	16.7/40.3	-	-
Dunne 2014	29	20	22.3	-	34.1
Funakoshi 2011	43.8	33.0	13.3	NA	100
Gaca 2011	-	18.9	-	49.8/6.8	51.5
Garcia 2013	51	14.3	-	-	12?
Grubitzsch 2014	56.4	-	-	36.9/31.5	15.2
Kang 2012	NA	29	NA	NA	100
Kiefer 2011	100	21.2	31.5	NA	-
Koeda 2013	11*	-	-	-	100
Korem 2014	48.6	19.4	-	-	77
Lalani 2010	44.9	16	20.7	NA	-
Lalani 2013	32.7	19.8	31.3	NA	83.8
Leontyev 2011	19.1	9.9	42.1	42.8/44.0	100
Leontyev 2012	67.1*	12.2	100	-/55.8	23.3
Machado 2014	-	-	-	-	100
Marks 2015	-	-	-	-	-
Musci 2010	23.2	7.1	64.8	63.9/20.3	100
Musci 2010b	25.2	14.1	77.8	69.7/24.2	-
	17.2	16.4	91.8	74.6/16.4	-
Ohara 2012	46	35	5	-	-
Ohara 2012	31	30	25	-	-
Pang 2015	44.0	13.1	10.5	- /22.5	45.5
Rasmussen 2010	27.9	19.5	8.8	-	-
Rouzé 2016	53	8	100	69/3	-
Sambola 2010	47	19	10	-	100
Spiliopoulos 2014	19.3*	21.5**	35.2	23.7/24.7	-
Thuny 2012	34	22	30	-	100
Wilbring 2012	6.5	16.1	100	-	-

* NYHA grade IV is categorized as congestive heart failure; ** all septic emboli included; Musci 2010b; Ohara 2012: native and prosthetic valve endocarditis are given separately
CHF: congestive heart failure; IE: infective endocarditis; urge/emerg: urgent/emergent

Table 5: hospital mortality with predictors

Author	hosp-mort (%)	predictor	OR	95%CI	p
Adademir 2013	15.5	female gender	5.6	1.3-25.0	0.022
		emergency	4.4	1.7-11.5	0.003
		postop ren. fail.	7.5	1.2-45.5	0.030
		LCOS	1.2	1.8-76.9	0.011
Alonso-Valle 2010	29 (operative: 6.5)	septic shock	42	4.9-357	0.001
		CHF	11	4.3-39.8	0.001
		Diagn delay > 3MO	7	1.0-47	0.047
		Resp failure	4.5	1.5-13.2	0.006
Barsic 2013	15.2	abscess	4.5	1.9-11.2	0.01
		Nosocomial	4.6	1.9-11.1	0.01
Caes 2014	13.0	age	1.1	1.0-1.1	0.03
		female gender	3.8	1.3-11.4	0.02
		prior cardiac surg	3.9	1.2-12.7	0.02
		creat > 2mg%	3.2	1.0-10.4	0.05
		S. aureus	4.0	1.3-12.4	0.02
		Emergency/salvage	11.8	2.8-50.3	0.001
		Conc CABG	4.3	1.2-16.2	0.03
Carugati 2013	30	age>60	2.2	1.3-3.8	0.01
		CKD	2.1	1.4-3.2	0.01
		Surgical indication	2.4	1.1-4.9	0.02
Chirouze 2015	48.4/23.3	age per year	1.03	1.01-1.05	0.007
		Stroke	2.9	1.7-5.1	0.002
		CHF/NYHA III-IV	2.0	1.1-3.5	0.016
Dunne 2014	12.9	age>65	5.6	-	0.013
Funakoshi 2011	5.2	early operation*			0.012
Gaca 2011	8.2	emergenct/salvage	3.2	3.0-3.3	0.001
		IABP/inotropics	2.0	1.9-2.0	0.001
		Cr>2.0	2.3	2.2-2.3	0.001
		Active IE	2.0	2.0-2.0	0.001
		17 more factors			

Garcia 2013	29.8	mod-severe stroke	1.6	1.2-2.2	0.001
		Charlson index	1.1	1.0-1.1	0.001
		Age (70)	1.6	1.3-2.0	0.001
		early IE	1.6	1.2-2.2	0.001
		S. aureus	2.3	1.7-2.9	0.001
		septic shock	2.2	1.7-3.0	0.001
		acute renal failure	1.7	1.3-2.0	0.001
		neurologic complic	1.6	1.8-3.1	0.001
		all ischemic complic	1.7	1.2-2.2	0.001
		>small isch complic	1.6	1.2-2.2	0.001
		Cerebral hemorrh	1.7	1.1-2.7	0.05
		CHF	2.4	1.8-2.3	0.001
Grubitzsch 2014	12.8	mechan support	3.8	1.7-8.4	0.001
		Interval surg>30d	3.1	1.2-8.1	0.019
		preop renal failure	2.3	1.1-4.8	0.02
Kiefer 2011	19.0 (all 4132 pts) With PA	NYHA III/IV	3.4	2.5-4.6	-
		age > 70	3.8	2.8-5.2	-
		Paravalv complic	1.7	1.4-2.0	-
		stroke	1.6	1.4-1.9	-
		diabetes mellitus	1.3	1.1-1.6	-
		Str. bovis	0.5	0.30.7	-
		surgery	0.8	0.6-1.0	-
Koeda 2013	9.2	Creat (per SD)	2.2	1.1-4.4	0.03
Korem 2014	33	age	1.1	1.0-1.1	0.001
Lalani 2010	5.9 (v. 11.2)	early surgery	0.44	0.33-0.59	0.001
Lalani 2013	22.0(v.26.7) With PA With PA + time dependent covariate	early surgery	0.68	0.53-0.87	0.03
			0.44	0.38-0.52	0.001
			0.90	0.76-1.07	0.24
Leontyev 2011	24.3 (PVE only)	sepsis	6.5	2.0-21.0	0.010
		LVEF<30	5.8	1.3-25.0	0.020
		concom CABG	3.3	1.1-9.8	0.030
		abscess	2.7	1.2-6.4	0.020
Leontyev 2012	25	sepsis	3.6	1.2-10.7	-
		Renal dysfunction	3.3	1.1-9.5	-
		Conc CABG	2.8	1.1-7.0	-
		PVE	2.4	1.1-5.6	-

Marks 2015	12.2	prior cardiac surgery	3.9	-	0.030
		neutrophil count	2.3	-	0.050
		serum albumin	0.9	-	0.040
		blood urea	2.6	-	0.001
Musci 2010	28.4 for PVE (32.4% early) (27.2% late)	mechan support	4.3	3.1-5.9	0.001
		emergency	2.1	1.3-3.5	0.003
		preop inotropics	1.8	1.3-2.5	0.001
		MVR	1.5	1.2-2.1	0.004
		Age	1.1	1.1-1.2	0.001
Ohara 2012	NVE 11	CHF	6.7	2.4-18.7	0.01
		S. aureus	3.5	1.3-9.7	0.02
		early surgery	0.1	0.03-0.2	0.01
Ohara 2012	PVE 22	age per 1y	1.1	1.0-1.2	0.03
		S. aureus	5.8	1.4-24.0	0.02
		CHF	7.4	1.8-30.7	0.01
Ota 2011		No predictor identified			
Pang 2015	6.3	creat clearance	0.9	0.9-1.0	0.001
		preop stroke	8.1	1.6-40.4	0.011
Rasmussen 2010	11 (surgery) 17 (deliberate medical) 29 (imposed medical)	cardiac surgery	0.4	0.2-0.7	0.003
Rouzé 2016	16	fistula	2.8	1.0-7.3	0.04
		MVR	3.2	1.2-8.7	0.02
		Renal failure	2.8	1.1-7.1	0.03
Sambola 2010	22	CHF	19.5	3.5-108.2	0.001
		Stroke	5.5	1.2-25.1	0.02
		Surgery	0.2	0.04-0.8	0.02
		acute renal failure	3.7	1.1-12.6	0.03
Spiliopoulos 2014	8.5	LCOS	5.5	-	0.010
Wilbring 2012	12.9	terminal renal fail	4.8		0.01
		diabetes type II	4.6		0.01
		postop renal fail	4.0		0.01
		staphylococcus	2.1		0.01

CABG: coronary artery bypass grafting; CHF: congestive heart failure; CI: confidence interval; CKD: chronic kidney disease; creat: creatinine; fail: failure; hemorrh: hemorrhage; hosp mort: hospital mortality; IE: infective endocarditis; LCOS: low cardiac output syndrome; LVEF: left ventricular ejection fraction; mechan: mechanical; MVR: mitral valve replacement; NYHA: New York Heart Association; OR: odds ratio; postop: postoperative; preop: preoperative; PA: propensity analysis; PVE: prosthetic valve endocarditis; >small isch complic: more than small ischemic complication