mineral density after 6 and 12 months of androgen deprivation therapy had not been evaluated. Ten trials fulfilled all the inclusion criteria[15-24]. Since one of these trials reported 2 treatment groups (orchiectomy, chemical castration), the data were regarded as 2 studies. **Table 1** shows the characteristics of the studies included in this analysis.

Most of the studies had used dual-energy x-ray absorptiometry to measure the bone mineral density of the femoral neck, the lumbar spine and the hip. One study had used dual-photon densitometry with a gadolinium radiation source. Two studies had used quantitative computed tomography to measure the bone mineral density of the lumbar spine. Two of the 11 studies examined the effects of orchiectomy, 1 study evaluated the effects of orchiectomy or chemical castration, and 8 studies evaluated the effects of chemical castration (GnRH agonist and/or antiandrogen). **Table 2**, **Table 3** and **Table 4** show a summary of the trial results.

2. Meta-analysis

Changes in the bone mineral density of the femoral neck for the androgen deprivation therapy group ranged between −0.6 and 6.5% decrease at 6 months and the weighted mean was 1.6% decrease with 95% confidence interval (CI) to be −0.8 to 4.0%. At 12 months, they ranged between −0.3 to 9.6% decrease and the weighted mean was 2.8% decrease with 95% CI to be 0.3 to 5.3%. For the lumbar spine, they ranged between 0.2 and 7.1% decrease (weighted mean decrease, 1.7%; 95% CI, −0.3 to 3.7%) at 6 months. At 12 months, they ranged between 0.5 and 4.6 % decrease (weighted mean decrease, 2.7%; 95% CI, −0.2 to 5.6%). For the hip, they ranged between −0.1 and 1.1% decrease (weighted mean decrease, 0.7%; 95% CI, −0.9 to 2.3%) at 6 months. At 12 months, they ranged between 0.4 and 3.3% decrease (weighted mean decrease, 1.5 %; 95% CI, −0.7 to 3.7%). Thus, the bone mineral density decreased at all the three sites according to the duration of the androgen deprivation therapy. The overall severity of the osteoporosis was represented by the differences in the bone mineral density after 6 or 12 months of therapy between the androgen deprivation therapy group and a control group, and the results were shown by using the effect size as follows; femoral neck, effect size 0.62 (95% CI, 0.24 to 0.99; P= 0.002), lumbar spine, effect size 0.58 (95% CI, 0.20 to 0.97; P=0.003), and hip, effect size 0.89 (95% CI, 0.47 to 1.32; P<0.001). These results are represented graphically in **Fig. 1**. In comparison with that in the control group, the bone mineral density at all the sites examined was significantly decreased after 6 or 12 months according to the use of androgen deprivation therapy.

Discussion

Although osteoporosis has long been considered as a disease of women, in the earliest reports of the epidemiology of osteoporosis, it was apparent that the classical age-related increase in the frequency of fractures seen in women is also evident in men. In fact, by World Health Organization criteria, the prevalence rates of osteoporosis at the hip, spine or wrist after age 50 years appears to be higher in women (35 %) than in men (19%). Yet, the actual prevalence rates of osteoporotic fracture do not differ between men (10%) and women (13%)[25]. These indicate that men have a higher risk of fracture than women with the same degree of decrease in bone mineral density. Moreover, one-seventh of all vertebral compression fractures and one-fourth to one-fifth of all hip fractures occur in men[26], and mortality related to hip fractures is higher in men than in women[27].

In a recent study, skeletal fractures in men with prostate cancer were negatively associated with the overall survival, independent of other prognostic factors[28]. Increasing duration of androgen deprivation therapy was significantly associated with increasing fracture risk in men with prostate cancer. Hip fractures are a major cause of disability and functional impairment. The results of our systematic review show that the bone mineral density (weighted mean) was decreased by 2.8% (0.3 to 5.3%) at the femoral neck, by 2.7 % (−0.2 to 5.6%) at the lumbar spine, and by 1.5% (−0.7 to 3.7%) at the hip after 12 months of androgen deprivation therapy. The rates of bone mineral loss about 2–3% per year, as estimated in the present study, should not be negligible, because the bone loss continuously progresses during the chronic androgen deprivation therapy: for example, the spinal bone mineral density values were 14% less, and the hip bone mineral density values were 28% less, than those observed in age-matched control individuals after 10 years of the therapy[29]. In contrast, the bone mineral density did not significantly change at any of these skeletal sites in the control group. Attention should therefore be focused on preventing osteoporosis in patients receiving androgen deprivation therapy. In normal men after the age of 55 years, the bone mineral density is reported to gradually increase via the formation of spinal osteophytes and calcification of paravertebral structures when measured by dual energy x-ray absorptiometry[30]. The present analysis, however, could not detect the age-related changes, probably because of the short follow-up period (6–12 months).

Androgen deprivation therapy is associated with a decrease in the levels of testosterone and dihydrotestosterone to castration levels. The hypogonadism has been reported to be a major risk factor for osteoporosis in adult men. Long-standing hypogonadism secondary to hyperprolactinemia has been shown to be associated with significant reductions in spinal and cortical bone density in men. Testosterone therapy given to adult men with acquired hypogonadism is associated with reduced bone remodeling and increase of trabecular bone density[31]. Thus, it was surmised that androgen deprivation therapy might cause osteoporosis. Androgens mediate osteoblast proliferation and differentiation, and increase bone matrix production and osteocalcin secretion, via the androgen receptors present on osteoblasts. Testosterone also modulates the effects of various growth factors, includ-

Table 1. Characteristics of the 11 Studies Included in the Review.

Study	Study quality	No of patients†	Mean age (years)	Type of prostate cancer	Technique	Precision (%)‡	Calcium supplement§	Type of androgen deprivation therapy	Study period (months)
Eriksson et al. 1995[15]	b	11	73.9	Localized	DPD	2.9	N.A.	Orchiectomy	12
Diamond et al. 1998[16]	b	11	78.2	Disseminated	DXA (femoral)	3.6 (femoral)	–	GnRH agonist and	6
					QCT (lumbar)	2.8 (lumbar)		antiandrogen	
Maillefert et al. 1999[17]	b	7	69.9	Stage C	DXA	1.5 (femoral)	–	GnRH agonist	6 and 12
						1.0 (lumbar)			
Daniell et al. 2000a[18]	b	10	76.8	Advanced or recurrent	DXA	1.2	+	Orchiectomy	12
Daniell et al. 2000b[18]	b	16	71.9	Advanced or recurrent	DXA	1.2	+	GnRH agonist and/or	12
								antiandrogen	
Diamond et al. 2001[19]	a	10	75.1	Metastatic	DXA (femoral)	0.8 (femoral)	–	GnRH agonist and/or	6
		10 (control)	71.5 (control)		QCT (lumbar)	2.8 (lumbar)		antiandrogen	
Smith et al. 2001[20]	a	22	65	Advanced or recurrent	DXA	N.A.	+	GnRH agonist	6 and 12
Preston et al. 2002[21]	b	36	73.4	N.A.	DXA	N.A.	+	Orchiectomy or	6 and 12
		34 (control)	71.8 (control)					GnRH agonist	
Mittan et al. 2002[22]	b	15	75	Localized	DXA	N.A. (femoral)	–	GnRH agonist	6 and 12
		13 (control)	70 (control)			1.0 (lumbar)			
						0.87 (hip)			
Berruti et al. 2002[23]	b	35	75	Localized	DXA	0.5 (lumbar)	+	GnRH agonist	6 and 12
						1.4 (hip)			
Smith et al. 2003[24]	a	34	70.2	Localized	DXA	N.A.	+	GnRH agonist and/or	12
								antiandrogen	

Data derived from prospective, randomized, controlled clinical trials on the bone effects of androgen deprivation therapy in patients with prostate cancer were judged as class a. Data from observational cohort studies or prospective, controlled clinical trials with missing randomization information were judged as class b. †Number of patients at the end of follow-up. ‡Precision is defined as the coefficient of variation for repeated measurement. §+: Standard supplement of 500 or 1000 mg calcium per day, –: No calcium supplement. DPD, dual photon densitometry; DXA, dual energy x-ray absorptiometry; QCT, quantitative computed tomography; N.A., not available.

Table 2. Changes in Bone Mineral Density at the Femoral Neck at 6 and 12 Months.

Study	Treatment arm	Percent changes at 6 months	Percent changes at 12 months
Eriksson et al. 1995[15]	ADT	N.A.	−9.6 ± 3.8
Diamond et al. 1998[16]		−6.5 ± 4.3	N.A.
Maillefert et al. 1999[17]		−2.7 ± 2.8	−3.9 ± 3.8
Daniell et al. 2000a[18]		N.A.	−2.3 ± 7.3
Daniell et al. 2000b[18]		N.A.	−3.8 ± 3.2
Diamond et al. 2001[19]		−3.2 ± 2.5	N.A.
Smith et al. 2001[20]		0.6 ± 2.8	0.3 ± 2.8
Preston et al. 2002[21]		−0.2 ± 2.5	−0.5 ± 3.6
Mittan et al. 2002[22]		0.0 ± 3.5	−2.3 ± 3.1
Smith et al. 2003[24]		N.A.	−2.1 ± 4.1
Pooled estimate†		**−1.6 (95% CI, −4.0 to 0.8) n = 105**	**−2.8 (95% CI, −5.3 to −0.3) n = 151**
Diamond et al. 2001[19]	CTL	−1.6 ± 1.9	N.A.
Preston et al. 2002[21]		1.2 ± 2.4	1.4 ± 3.5
Mittan et al. 2002[22]		−0.5 ± 2.2	0.0 ± 2.5

Changes in absolute values compared to basal values. Negative numbers indicate bone loss. Values are presented as the mean ± the standard deviation.

† Weighted mean. ADT, androgen deprivation therapy; CTL, control; N.A., not available; CI, confidence interval; n, number of patients.

Table 3. Changes in Bone Mineral Density at the Lumbar Spine at 6 and 12 Months.

Study	Treatment arm	Percent changes at 6 months	Percent changes at 12 months
Diamond et al. 1998[16]	ADT	−6.6 ± 5.0	N.A.
Maillefert et al. 1999[17]		−3.0 ± 3.2	−4.6 ± 3.6
Diamond et al. 2001[19]		−7.1 ± 5.4	N.A.
Smith et al. 2001[20]		−1.3 ± 1.4	−3.3 ± 3.2
Preston et al. 2002[21]		−0.2 ± 2.5	−0.5 ± 3.6
Mittan et al. 2002[22]		−1.6 ± 3.5	−2.8 ± 3.9
Berruti et al. 2002[23]		−1.4 ± 3.2	−2.3 ± 3.6
Smith et al. 2003[24]		N.A.	−2.2 ± 5.2
Pooled estimate†		**−1.7 (95% CI, −3.7 to 0.3) n = 140**	**−2.7 (95% CI, −5.6 to 0.2) n = 149**
Diamond et al. 2001[19]	CTL	0.9 ± 2.8	N.A.
Preston et al. 2002[21]		0.1 ± 1.8	0.3 ± 2.9
Mittan et al. 2002[22]		0.7 ± 2.9	0.4 ± 2.9

Changes in absolute values compared to basal values. Negative numbers indicate bone loss. Values are presented as the mean ± the standard deviation.

† Weighted mean. ADT, androgen deprivation therapy; CTL, control; N.A., not available; CI, confidence interval; n, number of patients.

ing transforming growth factor-β and insulin-like growth factor-I, which may be important for osteoblast proliferation. Thus, androgens are important factors to regulate the bone development and homeostasis.

Although testosterone is the major circulating androgen, there is evidence that its skeletal effects are mediated by the local production of estrogen intermediates. Aromatase, which is active in bone, converts testosterone to estradiol[32], and 5α-reductase reduces testosterone to androstendione and dihydrotestosterone[33]. A man with aromatase deficiency presents with delayed bone age, poor epiphyseal closure and tall stature. Estrogen treatment in these patients increased the spinal bone mineral density, and complete epiphyseal closure was achieved after nine months[34]. In contrast, testosterone has been shown to have no effect on skeletal maturation. Furthermore, a 28-year-old man with a point-mutation of the estrogen receptor gene which was associated with complete estrogen resistance exhibited severe defect of skeletal growth resulting in delayed epiphyseal closure and bone age, tall stature, increased bone turnover, and severely reduced bone mineral density for his chronological age[35]. In fact, estrogen receptors are expressed in both osteoblasts and osteoclasts[36]. These indicate that estrogen plays an important role in bone maturation and mineralization as much in men as in women.

Several treatment possibilities exist for osteoporosis asso-

Table 4. Changes in Bone Mineral Density at the Hip at 6 and 12 Months.

Study	Treatment arm	Percent changes at 6 months	Percent changes at 12 months
Smith et al. 2001[20]	ADT	−0.8 ± 1.9	−1.8 ± 1.9
Preston et al. 2002[21]		0.1 ± 1.8	−0.4 ± 2.4
Mittan et al. 2002[22]		−1.1 ± 1.2	−3.3 ± 3.1
Berruti et al. 2002[23]		−0.3 ± 1.8	−0.7 ± 2.3
Smith et al. 2003[24]		N.A.	−2.8 ± 3.5
Pooled estimate†		**−0.7 (95% CI, −2.3 to 0.9) n = 110**	**−1.5 (95% CI, −3.7 to 0.7) n = 142**
Preston et al. 2002[21]	CTL	1.3 ± 1.8	1.1 ± 1.7
Mittan et al. 2002[22]		0.0 ± 2.2	0.4 ± 1.4

Changes in absolute values compared to basal values. Negative numbers indicate bone loss. Values are presented as the mean ± the standard deviation.

† Weighted mean. ADT, androgen deprivation therapy; CTL, control; N.A., not available; CI, confidence interval; n, number of patients.

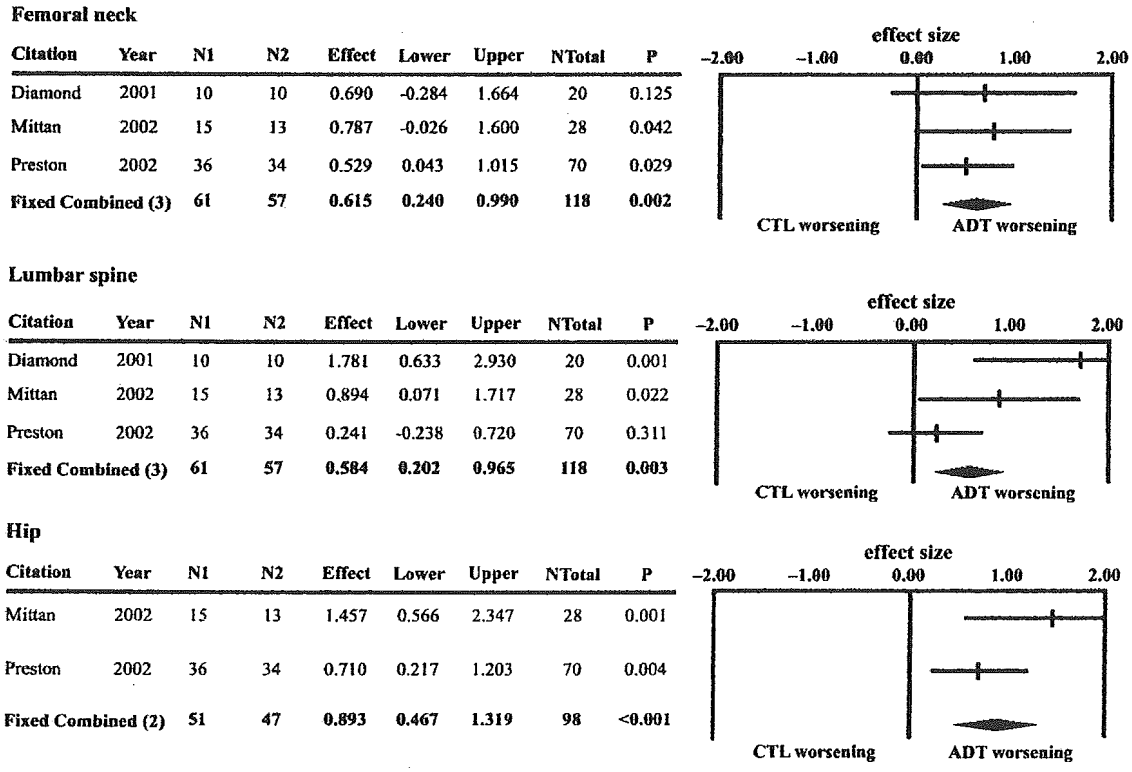


Fig. 1. Relative Risk of Change in Bone Mineral Density of the Femoral Neck, Lumbar Spine and Hip 12 Months after the Androgen Deprivation Therapy for Prostate Cancer.
Only the data from Diamond's study represent the change at 6 months because the data at 12 months are not available. A fixed-effect model was used to obtain a pooled effect size and 95% confidence interval (CI). N1, number of patients in the androgen-deprivation-therapy group (ADT). N2, number of patients in the control group (CTL). Effect, effect size. Lower and Upper, lower and upper 95% CI of effect size. NTotal, total sample size. P, statistical P value. Subtotal (Fixed Combined) values were obtained using the fixed effect model. Plot shows the meta-analytically pooled effect size (crossing point) with 95% CI (horizontal bar) or the combined effect size associated with 95% CI (rhombs).

ciated with androgen deprivation therapy. Medical castration with estrogens is not associated with bone loss in men with prostate cancer[15], although this treatment strategy has been abandoned because of the high rates of cardiovascular toxicity. Bisphosphonates may prevent or reverse some or all of the bone mineral density loss associated with androgen deprivation therapy. Smith et al. who randomized 43 men with nonlocalized or recurrent prostate cancer treated with leuprolide to receive intravenous pamidronate, found no change of the bone mineral density in the hip or the lumbar spine[20]. Thus, bisphosphonates may delay the progression of skeletal metastases arising from prostate cancer[17].

In conclusion, this study provides new and important information on osteoporosis during androgen deprivation therapy. The hormonal therapy seems to promote bone loss via multiple mechanisms. It would thus be reasonable to measure the bone mineral density in all men prior to the commencement of androgen deprivation therapy. Calcium and vitamin D supplementation and advice for abstinence from smoking and alcohol are suitable first-line preventive measures against bone loss under this condition. Treatment with bisphosphonates may also be a possible strategy to prevent bone loss, although further research is needed to explore the effects of bisphosphonates.

References

1) A. Jemal, T. Murray, A. Samuels, A. Ghafoor, E. Ward, M.J. Thun, Cancer statistics, 2003, *CA. Cancer J. Clin.*, **53**, 5–26 (2003).
2) C. Huggins, C.V. Hodges, Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate, *Cancer Res.*, **1**, 293–297 (1941).
3) The Medical Research Council Prostate Cancer Working Party Investigators Group, Immediate versus deferred treatment for advanced prostatic cancer : initial results of the Medical Research Council Trial, *Br. J. Urol.*, **79**, 235–246 (1997).
4) H.W. Daniell, Osteoporosis after orchiectomy for prostate cancer, *J. Urol.*, **157**, 439–444 (1997).
5) C.H. Kasperk, J.E. Wergedal, J.R. Farley, T.A. Linkhart, R.T. Turner, D.J. Baylink, Androgens directly stimulate proliferation of bone cells in vitro, *Endocrinology*, **124**, 1576–1578 (1989).
6) C.C. Pilbeam, L.G. Raisz, Effects of androgens on parathyroid hormone and interleukin-1-stimulated prostaglandin production in cultured neonatal mouse calvariae, *J. Bone Miner. Res.*, **5**, 1183–1188 (1990).
7) D.J. Benz, M.R. Haussler, M.A. Thomas, B. Speelman, B.S. Komm, High-affinity androgen binding and androgenic regulation of alpha 1 (I)-procollagen and transforming growth factor-beta steady state messenger ribonucleic acid levels in human osteoblast-like osteosarcoma cells, *Endocrinology*, **128**, 2723–2730 (1991).
8) D.S. Colvard, E.F. Eriksen, P.E. Keeting, E.M. Wilson, D.B. Lubahn, F.S. French, B.L. Riggs, T.C. Spelsberg, Identification of androgen receptors in normal human osteoblast-like cells, *Proc. Natl. Acad. Sci. USA*, **86**, 854–857 (1989).
9) N. Kelepouris, K.D. Harper, F. Gannon, F.S. Kaplan, J. G. Haddad, Severe osteoporosis in men, *Ann. Intern. Med.*, **123**, 452–460 (1995).
10) Y. Suzuki, Y. Ichikawa, E. Saito, M. Homma, Importance of increased urinary calcium excretion in the development of secondary hyperparathyroidism of patients under glucocorticoid therapy, *Metabolism*, **32**, 151–156 (1983).
11) G.A. Gronowicz, M.B. McCarthy, Glucocorticoids inhibit the attachment of osteoblasts to bone extracellular matrix proteins and decrease beta 1-integrin levels, *Endocrinology*, **136**, 598–608 (1995).
12) T.J. Hahn, V.C. Boisseau, L.V. Avioli, Effect of chronic corticosteroid administration on diaphyseal and metaphyseal bone mass, *J. Clin. Endocrinol. Metab.*, **39**, 274–282 (1974).
13) O. Schaadt, H. Bohr, Bone mineral in lumbar spine, femoral neck and femoral shaft measured by dual photon absorptiometry with 153-gadolineum in prednisone treatment, *Adv. Exp. Med. Biol.*, **171**, 201–208 (1984).
14) American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis, Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis : 2001 update, *Arthritis Rheum.*, **44**, 1496–1503 (2001).
15) S. Eriksson, A. Eriksson, R. Stege, K. Carlstrom, Bone mineral density in patients with prostatic cancer treated with orchidectomy and with estrogens, *Calcif. Tissue Int.*, **57**, 97–99 (1995).
16) T. Diamond, J. Campbell, C. Bryant, W. Lynch, The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma : longitudinal evaluation and response to intermittent cyclic etidronate therapy, *Cancer*, **83**, 1561–1566 (1998).
17) J.F. Maillefert, J. Sibilia, F. Michel, C. Saussine, R.M. Javier, C. Tavernier, Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma, *J. Urol.*, **161**, 1219–1222 (1999).
18) H.W. Daniell, S.R. Dunn, D.W. Ferguson, G. Lomas, Z. Niazi, P.T. Stratte, Progressive osteoporosis during androgen deprivation therapy for prostate cancer, *J. Urol.*, **163**, 181–186 (2000).
19) T.H. Diamond, J. Winters, A. Smith, P. De Souza, J.H. Kersley, W.J. Lynch, C. Bryant, The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade : a double blind, randomized, placebo-controlled crossover study, *Cancer*, **92**, 1444–1450 (2001).
20) M.R. Smith, F.J. McGovern, A.L. Zietman, M.A. Fallon, D.L. Hayden, D.A. Schoenfeld, P.W. Kantoff, J.S.

Finkelstein, Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer, *N. Engl. J. Med.*, **345**, 948–955 (2001).

21) D.M. Preston, J.I. Torrens, P. Harding, R.S. Howard, W.E. Duncan, D.G. Mcleod, Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss, *Prostate Cancer Prostatic Dis.*, **5**, 304–310 (2002).

22) D. Mittan, S. Lee, E. Miller, R.C. Perez, J.W. Basler, J. M. Bruder, Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs, *J. Clin. Endocrinol. Metab.*, **87**, 3656–3661 (2002).

23) A. Berruti, L. Dogliotti, C. Terrone, S. Cerutti, G. Isaia, R. Tarabuzzi, G. Reimondo, M. Mari, P. Ardissone, S. De Luca, G. Fasolis, D. Fontana, S.R. Rossetti, A. Angeli, Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy, *J. Urol.*, **167**, 2361–2367 (2002).

24) M.R. Smith, J. Eastham, D.M. Gleason, D. Shasha, S. Tchekmedyian, N. Zinner, Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer, *J. Urol.*, **169**, 2008–2012 (2003).

25) L.J. Melton, Ⅲ, E.J. Atkinson, M.K. O'Connor, W.M. O'Fallon, B.L. Riggs, Bone density and fracture risk in men, *J. Bone Miner. Res.*, **13**, 1915–1923 (1998).

26) J.A. Jackson, M. Kleerekoper, Osteoporosis in men: diagnosis, pathophysiology, and prevention, *Medicine*, **69**, 137–152 (1990).

27) G. Poor, E.J. Atkinson, W.M. O'Fallon, L.J. Melton, Ⅲ, Determinants of reduced survival following hip fractures in men, *Clin. Orthop.*, **319**, 260–265 (1995).

28) M.G. Oefelein, V. Ricchiuti, W. Conrad, M.I. Resnick, Skeletal fractures negatively correlate with overall survival in men with prostate cancer, *J. Urol.*, **168**, 1005–1007 (2002).

29) B.J. Kiratli, S. Srinivas, I. Perkash, M.K. Terris, Progressive decrease in bone density over 10 years of androgen deprivation therapy in patients with prostate cancer, *Urology*, **57**, 127–132 (2001).

30) E.S. Orwoll, S.K. Oviatt, T. Mann, The impact of osteophytic and vascular calcifications on vertebral mineral density measurements in men, *J. Clin. Endocrinol. Metab.*, **70**, 1202–1207 (1990).

31) L. Katznelson, J.S. Finkelstein, D.A. Schoenfeld, D.I. Rosenthal, E.J. Anderson, A. Klibanski, Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism, *J. Clin. Endocrinol. Metab.*, **81**, 4358–4365 (1996).

32) H. Nawata, S. Tanaka, S. Tanaka, R. Takayanagi, Y. Sakai, T. Yanase, S. Ikuyama, M. Haji, Aromatase in bone cell: association with osteoporosis in postmenopausal women, *J. Steroid Biochem. Mol. Biol.*, **53**, 165–174 (1995).

33) H.U. Schweikert, W. Rulf, N. Niederle, H.E. Schafer, E. Keck, F. Kruck, Testosterone metabolism in human bone, *Acta Endocrinol.*, **95**, 258–264 (1980).

34) C. Carani, K. Qin, M. Simoni, M. Faustini-Fustini, S. Serpente, J. Boyd, K.S. Korach, E.R. Simpson, Effect of testosterone and estradiol in a man with aromatase deficiency, *N. Engl. J. Med.*, **337**, 91–95 (1997).

35) E.P. Smith, J. Boyd, G.R. Frank, H. Takahashi, R.M. Cohen, B. Specker, T.C. Williams, D.B. Lubahn, K.S. Korach, Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man, *N. Engl. J. Med.*, **331**, 1056–1061 (1994).

36) M.J. Oursler, L. Pederson, L. Fitzpatrick, B.L. Riggs, T. Spelsberg, Human giant cell tumors of the bone (osteoclastomas) are estrogen target cells, *Proc. Natl. Acad. Sci. USA*, **91**, 5227–5231 (1994).

37) S. Boissier, M. Ferreras, O. Peyruchaud, S. Magnetto, F.H. Ebetino, M. Colombel, P. Delmas, J.M. Delaisse, P. Clezardin, Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases, *Cancer Res.*, **60**, 2949–2954 (2000).

臨床薬理 Jpn J Clin Pharmacol Ther Vol.36 No.2 p.69-79 Mar 2005〔別 刷〕

Comparison of Cilostazol and Ticlopidine Coadministered with Aspirin for Long-Term Efficacy and Safety after Coronary Stenting ; a Meta-Analysis

Masayuki HASHIGUCHI Keiko OHNO Satoshi KISHINO
Mayumi MOCHIZUKI and Tsuyoshi SHIGA

発行所 日本臨床薬理学会 TEL. 03-3815-1761

Comparison of Cilostazol and Ticlopidine Coadministered with Aspirin for Long-Term Efficacy and Safety after Coronary Stenting ; a Meta-Analysis

Masayuki HASHIGUCHI*1,2 Keiko OHNO*1 Satoshi KISHINO*1
Mayumi MOCHIZUKI*2 and Tsuyoshi SHIGA*3

*1 Department of Medication Use Analysis and Clinical Research, Meiji Pharmaceutical University, Tokyo, Japan
*2 Division for Evaluation and Analysis of Drug Information, Center of Clinical Pharmacy and Clinical Sciences, School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan
*3 Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan

Aims : To compare cilostazol with ticlopidine for long-term efficacy and safety as an adjunctive antiplatelet therapy after coronary stenting.

Methods : Using published clinical studies retrieved through Medline and other databases from 1986-2004, meta-analyses were employed to evaluate efficacy and adverse clinical events for cilostazol or ticlopidine coadministered with aspirin after coronary stenting. Major adverse cardiac events (MACE), quantitative coronary angiographic parameters (QCA) including minimal lumen diameter (MLD), late loss, loss index of diseased vessels, and net gain, or adverse clinical events after coronary stenting were compared between the two study arms and expressed with the mean difference or odds ratios (OR) specific for the individual studies and meta-analytic pooled estimate for the mean difference or OR.

Results : Five of the clinical studies we reviewed met the inclusion criteria and underwent meta-analysis. The cilostazol was found to be superior in the pooled estimate of the total clinical outcomes and QCA as compared to ticlopidine (OR [95% CI] : 0.59 [0.46, 0.75]), MLD (WMD [95% CI] : 0.27 mm [0.17, 0.37]), late loss (WMD [95% CI] : −0.36 mm [−0.51, −0.22]), loss index (WMD [95% CI] : −0.16 [−0.24, −0.08]), and net gain (WMD [95% CI] : 0.49 mm [0.30, 0.68]). The pooled estimate of all adverse clinical events in cilostazol was approximately the same as that seen for ticlopidine.

Conclusions : Our results suggest that cilostazol plus aspirin therapy, as compared to ticlopidine plus aspirin therapy, might be superior with regard to long-term efficacy, particularly in preventing late restenosis. Although cilostazol exhibits few serious adverse clinical events, we must pay attention to increased heart rate or the occurrence of arrhythmias during treatments.

Key words : cilostazol, ticlopidine, efficacy, safety, adverse event, antiplatelet therapy, intracoronary, stent implantation, meta-analysis

Introduction

Coronary stenting is reported to reduce restenosis after balloon coronary angioplasty[1-3]. Currently, coronary stenting has become an established treatment for coronary artery disease and is widely utilized in interventional cardiology. Moreover, use of adjunctive antiplatelet agents has been found to decrease stent-associated thrombosis, and play a role in improving final outcomes[3]. However, the prevention of stent-associated complications remains an important concern during the performance of coronary stenting, even though the overall success rate for the procedure has improved. Complications comprise : 1) acute vessel occlusion/closure due to thrombus formation occurring from immediately following to within 24 hours of the procedure ; 2) subacute thrombosis occurring between 1 and 30 days after stenting ; and 3) late coronary restenosis caused by intimal hyperplasia

Address for correspondence : HASHIGUCHI M. Division for Evaluation and Analysis of Drug Information, Center of Clinical Pharmacy and Clinical Sciences, School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan
(Manuscript received April 12, 2004 ; revised October 7, 2004 and November 25, 2004 ; accepted November 26, 2004)

or proliferation of smooth muscle cells secondary to growth factors released from platelets, occurring between 3 weeks and 6 months after stent placement. Aspirin, one of the most popular oral antiplatelet agents, has been shown to reduce the frequency of ischemic complications, including coronary occlusion/thrombosis after coronary angioplasty[3], but has no affect on restenosis[4]. Moreover, no optimum dose or duration of aspirin therapy following coronary stenting has been established.

Ticlopidine, an oral thienopyridine, is a potent inhibitor of platelet aggregation, exhibits a maximum platelet inhibition 3 to 5 days after initiation, and is associated with a platelet aggregation recovery that is slow once the drug is discontinued[5,6]. From the Stent Anticoagulation Restenosis Study (STARS) data, the combination of aspirin and ticlopidine following coronary stenting was shown to have lower rates of subacute thrombosis than that seen with aspirin use alone[7]. However, ticlopidine has a number of severe adverse clinical events, including agranulocytosis, hepatic impairment, and thrombotic thrombocytopenic purpura (TTP).

Cilostazol is another potent oral antiplatelet agent with a more rapid onset of action that selectively inhibits phosphodiesterase III, and is associated with a lower incidence of adverse effects[8-14]. In a prospective study of coronary stenting with concomitant aspirin and cilostazol, no thrombosis was observed even though cases of emergency stent placement were included[12]. Two interesting small randomized studies comparing cilostazol and aspirin suggested that cilostazol might reduce the incidence of late restenosis with the exception of thrombosis[15,16]. Adjunctive use of cilostazol with coronary stenting is thus becoming a more respected option[17]. To date, several clinical trials comparing ticlopidine and cilostazol as adjunctive antiplatelet agents after coronary stenting have been reported, but most such trials have utilized only small subject populations.

In a previous study, we used meta-analysis to document the effectiveness of a 1-month administration of cilostazol as compared to ticlopidine after elective coronary stenting[18]. In the current study, we further compare cilostazol and ticlopidine by using a systematic review of the literature and meta-analysis techniques in order to evaluate the long-term efficacy and safety with regard to the clinical outcome of cilostazol use after coronary artery stent implantation.

Methods

1. Literature search

A comprehensive literature search was conducted using the Medline database (Pubmed®). All clinical studies that were published on Medline between January 1986 and March 2004 were examined. For Medline searches, a combination of the keywords "cilostazol" and "ticlopidine" was used with searches using the MeSH subject headings "stents", "thrombosis" or "coronary restenosis". We attempted to identify all clinical studies in both the English and Japanese languages. In addition to the search of the electronic database, manual searches were undertaken using reference lists from retrieved articles. In addition, several content experts and pharmaceutical companies were consulted for information about the existence of unpublished or recent studies.

2. Inclusion criteria

Two investigators (MH, KO) examined the title and abstract of each paper, and then the full paper if necessary. To be included in this meta-analysis, the study had to meet all the following criteria : prospective or retrospective, clinical study of adults after intracoronary artery stent implantation, including data from patients who successfully had their coronary artery stent implantation terminated, had an efficacy evaluation using coronary artery angiography, and had a clinical follow-up period of more than 6 months that evaluated the clinical outcome.

3. Assessment of the quality of literature

We evaluated the quality of the literature using the score system developed by Morizane[19], which is similar to a procedure that was adopted by Downs & Black[20], and Cho & Bero[21]. Seven major items were evaluated for each study : study hypothesis, patient selection, patient characteristics, number of study patients, randomization and blinding, measurements and definition of outcome, and statistical method. Quality was graded for each of the seven items on a scale of 0-15 (total maximum score= 100). Each item that was evaluated had a different

maximal score due the nature of the item. In order to evaluate the quality of the studies, three investigators (MH, KO, TS) independently evaluated the total scores for each of the respective studies. Differences were resolved by consensus. The quality of the studies was classified as follows, high (greater than 70 points), moderate (40 to 69 points), and low (less than 40 points).

4. Data extraction

We extracted the data for the clinical study design used, patient characteristics, implanted stent materials, the follow-up periods, antiplatelet drug and dose or dosage, and duration of drug administration. For the outcome following stent placement, we assessed major adverse cardiac events (MACE) such as death and myocardial infarction (MI), rates of acute occlusion/thrombosis occurring within 24 hours or subacute thrombosis/restenosis occurring up to 1 month after the procedure, angiographic late restenosis (defined as diameter stenosis>50% at the 6-month follow-up) and additional target lesion revascularization (TLR) that was clinically needed. We also compared minimal lumen diameter of diseased vessels (MLD), late loss, loss index, or net gain with quantitative coronary angiography (QCA) between the time point immediately after stent placement and the 6 subsequent months. To evaluate the adverse clinical events linked to the treatment, we assessed rates of bleeding, intracranial hemorrhage, vascular complication, leukopenia, thrombocytopenia or neutropenia, skin rash, gastro-intestinal disturbance, hepatic impairment (elevated aminotransferase), and arrhythmia during the follow-up period.

5. Statistical analysis

For clinical outcomes such as for MACE and adverse clinical events, we used a ratio where data were expressed by an odds ratio (OR) and 95% confidence interval (CI). Statistical significance was judged using OR and 95% CI. Thus if the 95% CI did not include 1, the data indicated the presence of statistical significance. For the efficacy on QCA (MLD, late loss, loss index, and net gain), the parameters were treated as a continuous variable and analyzed by a general variance-based method where data are expressed as the weighted mean difference (WMD) and 95% CI, with statistical significance judged using the WMD and 95% CI. Thus, if the 95% CI did not include 0, the data indicated the presence of statistical significance. A test for homogeneity of pooled estimates of the data was performed using a Q statistic, which is referred to as a chi-square distribution with the degrees of freedom equal to the total number of studies minus 1. Statistical significance was expressed at the level of $p<0.05$. The random effect model (DerSimonian-Laird method) was used for the pooled estimates where homogeneity was not observed for the data. In cases where homogeneity was observed, a fixed effect model (Peto method) was used for the pooled estimates. To avoid problems of bias and instability associated with estimation of ORs, 0.5 was added to each cell of the four-fold table. Meta-analytical calculations were performed using Excel 2000 software (Microsoft Corporation, Redmond, WA, USA).

Results

1. Data abstraction

Table shows the summary for the 5 studies that met the criteria for inclusion in this study. All studies that dealt with comparisons of cilostazol plus aspirin vs. ticlopidine plus aspirin, were published between 1999 and 2002, and included 6-12 months of follow-up period. The doses of aspirin ranged from 81 to 243 mg/day ; that for ticlopidine ranged from 200 to 500 mg/day, and that for cilostazol was 200 mg/day. Of the included data groups, 1 was a retrospective observational study while the other 4 were randomized open-label controlled studies.

2. Assessment of the quality of literature

In 4 out of 5 studies the results for the quality score of the literature were scored as being of high quality (>70 points) ; Kamishirado et al.[22] (77 points), Kozuma et al.[23] (73 points), Park et al.[24] (79 points), and Ochiai et al.[25] (71 points). The remaining study was scored as being of moderate quality (40-69 points) and was reported by Tanabe et al.[26] (52 points). All studies were judged as being of appropriate literature quality with regard to the combination of the data for meta-analysis. Accordingly, a total of 823 patients with 930 lesions were included in the present analysis.

Table Summary of five clinical studies for comparison of cilostazol and ticlopidine

Reference	Study design	Clinical follow-up (mo)	Study drug, Dose(mg/day), Duration(mo)	Post-heparin therapy	Age (yrs) (mean±SD)
Kamishirado et al., 2002	RCT	6	CLZ(200)+ASA(81)6 mos vs TCL(200)+ASA(81)6 mos	No	65±10 69±9
Kozuma et al., 2001	RCT	12	CLZ(200)6 mos+ASA(81-162), NR vs TCL(200)6 mos+ASA(81-162), NR	No	62±9 62±10
Tanabe et al., 2001	Retrospective, Observational	6	CLZ(200)+ASA(81)4-6 mos vs TCL(200)+ASA(243)4-6 mos	Yes	68±9 66±8
Park et al., 2000	RCT	6	CLZ(200)6 mos+ASA(200) indefinitely vs TCL(500)1 mo+ASA(200) indefinitely	No	59±9 59±9
Ochiai et al., 1999	RCT	6	CLZ(200)6 mos+ASA(243)6 mos vs TCL(200)1 mo+ASA(243)6 mos	Yes	61±10 60±14

ASA : aspirin, TCL : ticlopidine, CLZ : cilostazol, RCT : randomized controlled trial, *ACS : acute coronary syndrome including emergencies, P : Palmaz-Schatz, G : GFX, N : NIR, M : MultiLink, W : Wiktor, C : CrossFlex, NR : not reported

3. Long-term efficacy of cilostazol vs. ticlopidine

Fig. 1 shows the OR for MACE for the clinical outcome between cilostazol and ticlopidine. With regard to the occurrence of serious cases of MACE, there were no significant differences between the two therapies for death and MI. For the rate of the stent-associated complications of acute or subacute thrombosis there were also no significant differences. However, for the rates of late restenosis and additional TLR needed by patients, the numbers were significantly lower for cilostazol as compared to those for patients receiving ticlopidine (OR [95% CI] : 0.60 [0.43, 0.83] for late restenosis, 0.54 [0.33, 0.89] for additional TLR). The pooled estimates obtained by combining all outcomes documented the superiority of cilostazol over ticlopidine administration (OR [95% CI] : 0.59 [0.46, 0.75]).

Fig. 2 shows the differences between the two therapies for changes in each QCA (MLD, late loss, loss index, and net gain) as seen at the end of the study. The WMD [95%CI] results of the meta-analysis for MLD (0.27 mm [0.17, 0.37]), late loss (−0.36 mm [−0.51, −0.22]) and loss index (−0.16 [−0.24, −0.08]) indicated a statistically significant difference with regard to the benefit of the combined cilostazol with aspirin therapy versus the combined ticlopidine with aspirin therapy. The results of the meta-analysis for net gain (WMD [95% CI] : 0.49 mm [0.30, 0.68]) also showed a statistically significant difference regarding the benefit of combined cilostazol with aspirin therapy versus combined ticlopidine with aspirin therapy, although only two papers contained statements about the net gain.

4. Adverse clinical events of cilostazol vs. ticlopidine

Figure 3 shows the OR for adverse clinical events between the two therapies. The results of the meta-analysis for all events except for elevated aminotransferase showed no statistically significant differences between the therapies. Also, pooled estimates obtained by combining all events documented no statistically significant difference between the therapies (OR [95% CI] ; 0.80 [0.47, 1.35]), which suggests that the combination of cilostazol plus aspirin does not differ from that of ticlopidine plus aspirin.

No. of pts. (male/female)	No. of lesions	Elective or ACS*	Type of stent
65 (53/12)	65	Elective	P, G, N, M, W
65 (54/11)	65		
65 (61/4)	71	Elective	P
65 (51/14)	67		
54 (38/16)	63	Elective + ACS	P, W, G, M
50 (38/12)	55		
208 (148/60)	254	Elective	C, G, N
201 (151/50)	240		
25 (20/5)	25	ACS	P
25 (20/5)	25		

Discussion

We evaluated the long-term efficacy and safety with regard to clinical outcome for the oral antiplatelet agents cilostazol or ticlopidine after intracoronary artery stent implantation by systematically reviewing the literature and using meta-analysis techniques. The quality of all studies used had high to moderate scores (52 to 79 points) according to the score system for the validity of literature in clinical trials. The reason that the scores did not have extremely high point numbers may be related to the fact that 4 studies were open-label studies and 1 study was a retrospective observational study.

Meta-analysis of acute and late outcomes demonstrated superiority in the prevention of restenosis and reduction of additional TLR in patients with cilostazol plus aspirin versus that seen for ticlopidine plus aspirin administrations, even though we observed no differences in the outcomes for the other categories of MACE. These results suggest that cilostazol may have an additive preventive effect against late restenosis, which is in part caused by intimal hyperplasia or smooth muscle cell proliferation. This protective effect may be due to cilostazol's thrombotic preventive effect. In the comparison between the two therapies with regard to the evaluation of QCA (Fig. 2), cilostazol plus aspirin was also found to have a beneficial effect in MLD, late loss, loss index, and net gain versus that seen with ticlopidine plus aspirin.

The exact reason for these different effects between these two therapies is unclear, but other factors need to be considered. First, the follow-up and administration periods for the drugs in these studies were varied ; 4-6 months in Tanabe et al.[26], and 6 months in Kamishirado et al.[22], Kozuma et al.[23], Park et al.[24], and Ochiai et al.[25]. Additionally, for the latter two studies, (Park et al.[24] and Ochiai et al.[25]), ticlopidine was administered for only 1 month, a time period that was much shorter than for that seen with cilostazol. We also found a tendency in our analyses of MLD that the administration of cilostazol for 6 months was superior to that of the 1 month, 4-6, or 6 months of ticlopidine administration. These results suggest that the combination therapy of cilostazol plus aspirin may be effective in maintaining the diameter of vessels for a long time after stent implantation, but only when cilostazol is administered for 6 months, which coincides with the peak incidence of late restenosis. Secondly, the results might be related to a differing pharmacological effects between cilostazol and ticlopidine. It is known that neointimal formation plays a major role in the restenotic process in stented coronary segments. Cilostazol has many mechanisms that may inhibit smooth muscle cell proliferation including acting on the phosphodiesterase III receptors[26,27], heparin-binding epidermal growth factor-like growth factor[28], or platelet-derived growth factors[29]. These mechanisms of cilostazol may play a part in the role of the inhibition of the restenosis process that occurs after coronary stenting.

In most studies, antiplatelet agents were started a few days before the coronary stenting. Ticlopidine and cilostazol was begun 2 days prior in Kamishirado et al.[22], and Park et al.[24], while in Tanabe et al.[26], ticlopidine was started 4 days and cilostazol 2 days prior to the stenting. Cilostazol is known to achieve a maximum antiplatelet effect within 1 day[30], while ticlopidine needs at least 2 days to reach effective therapeutic concentrations *in*

Reference	CLZ n/N	TCL n/N	Clinical outcomes	OR [95% CI]
1) Death				
Kamishirado et al., 2002	0/65	1/65		0.33 [0.01, 8.21]
Kozuma et al., 2001	0/53	1/52		0.32 [0.01, 8.06]
Tanabe et al., 2001	0/54	0/50		0.93 [0.02, 47.58]
Park et al., 2000	2/208	4/201		0.48 [0.09, 2.64]
Ochiai et al., 1999	2/25	2/25		1.00 [0.13, 7.72]
Total	4/405	8/393		0.57 [0.20, 1.58][a)]
2) Myocardial infarction				
Kamishirado et al., 2002	0/65	0/65		1.00 [0.02, 51.16]
Kozuma et al., 2001	0/53	1/52		0.32 [0.01, 8.06]
Park et al., 2000	15/208	21/201		0.67 [0.33, 1.33]
Total	15/326	22/318		0.65 [0.34, 1.26][a)]
3) Acute stent thrombosis				
Kamishirado et al., 2002	0/65	0/65		1.00 [0.02, 51.16]
Tanabe et al., 2001	0/54	0/50		0.93 [0.02, 47.58]
Park et al., 2000	0/208	0/201		0.97 [0.02, 48.94]
Total	0/327	0/316		0.96 [0.10, 9.27][a)]
4) Subacute stent thrombosis				
Kamishirado et al., 2002	0/65	2/65		0.19 [0.01, 4.12]
Kozuma et al., 2001	0/59	1/60		0.33 [0.01, 8.35]
Tanabe et al., 2001	0/54	0/50		0.93 [0.02, 47.58]
Park et al., 2000	0/208	0/201		0.97 [0.02, 48.94]
Total	0/386	3/376		0.42 [0.09, 1.84][a)]
5) Late restenosis				
Kamishirado et al., 2002	7/54	17/57		0.35 [0.13, 0.93]
Tanabe et al., 2001	9/63	18/55		0.34 [0.14, 0.85]
Park et al., 2000	58/254	65/240		0.80 [0.53, 1.20]
Ochiai et al., 1999	0/25	5/25		0.07 [0.01, 1.40]
Total	74/396	105/377		0.60 [0.43, 0.83][a)]
6) Additional TLR				
Kamishirado et al., 2002	4/54	12/57		0.30 [0.09, 0.99]
Kozuma et al., 2001	3/56	3/58		1.04 [0.20, 5.37]
Tanabe et al., 2001	7/63	11/55		0.50 [0.18, 1.40]
Park et al., 2000	11/208	13/201		0.81 [0.35, 1.85]
Ochiai et al., 1999	0/25	4/25		0.09 [0.01, 1.84]
Total	25/406	43/396		0.54 [0.33, 0.89][a)]
Total clinical outcomes	118/2246	181/2176		0.59 [0.46, 0.75][a)]

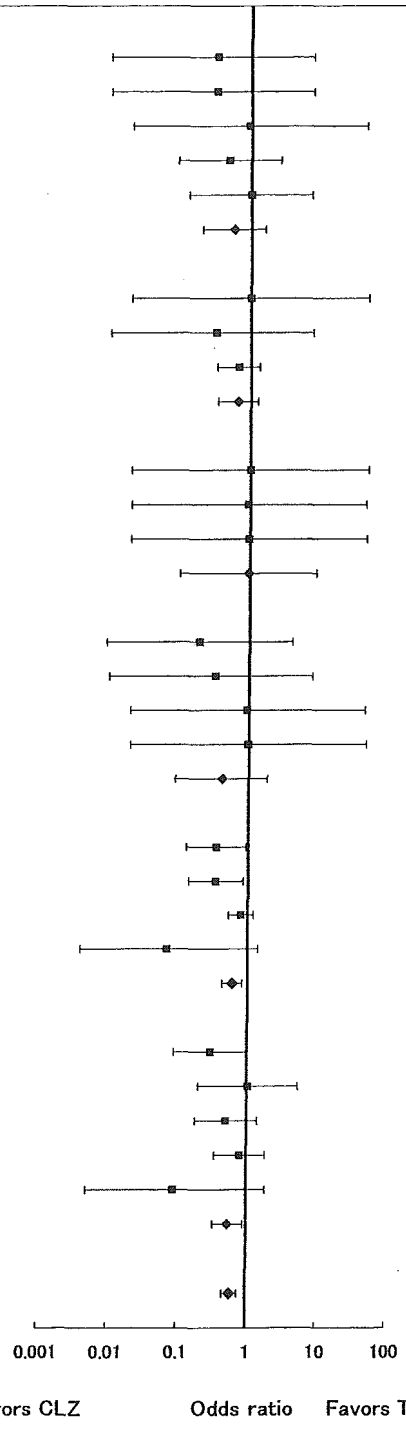
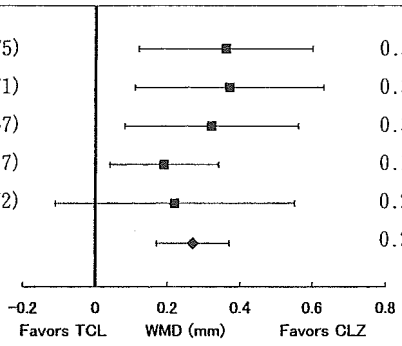


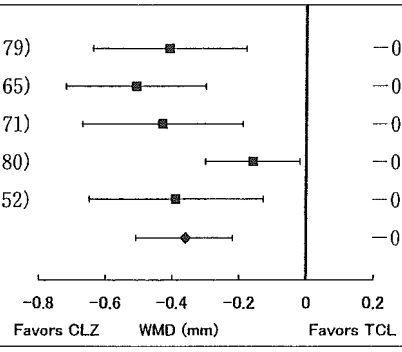
Fig. 1 The odds ratio for MACE for the outcome between the combined ticlopidine with aspirin therapy and the combined cilostazol with aspirin therapy

TCL : ticlopidine, CLZ : cilostazol, OR : odds ratio, TLR : target lesion revascularization, n : number of patients who reported the outcome, N : total number of patients, [a)]Peto method

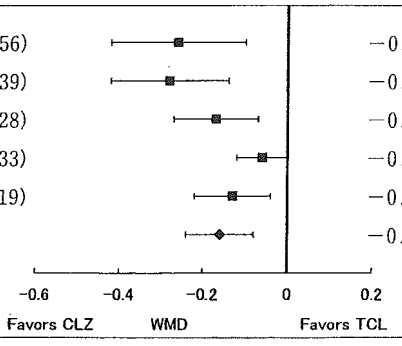
Reference	CLZ n	CLZ Mean (SD)	TCL n	TCL Mean (SD)	MLD (mm)	WMD [95% CI]
Kamishirado et al., 2002	54	2.35 (0.53)	57	1.99 (0.75)		0.36 [0.12, 0.60]
Kozuma et al., 2001	61	1.95 (0.72)	58	1.58 (0.71)		0.37 [0.11, 0.63]
Tanabe et al., 2001	63	2.09 (0.66)	55	1.77 (0.67)		0.32 [0.08, 0.56]
Park et al., 2000	254	2.12 (0.87)	240	1.93 (0.87)		0.19 [0.04, 0.34]
Ochiai et al., 1999	25	2.24 (0.42)	25	2.02 (0.72)		0.22 [−0.11, 0.55]
Total	457	2.15	435	1.86		0.27 [0.17, 0.37][a]



Reference	CLZ n	CLZ Mean (SD)	TCL n	TCL Mean (SD)	Late loss (mm)	WMD [95% CI]
Kamishirado et al., 2002	54	0.28 (0.40)	57	0.69 (0.79)		−0.41 [−0.64, −0.18]
Kozuma et al., 2001	61	0.58 (0.52)	58	1.09 (0.65)		−0.51 [−0.72, −0.30]
Tanabe et al., 2001	63	0.84 (0.62)	55	1.27 (0.71)		−0.43 [−0.67, −0.19]
Park et al., 2000	254	1.14 (0.77)	240	1.30 (0.80)		−0.16 [−0.30, −0.02]
Ochiai et al., 1999	25	0.49 (0.40)	25	0.88 (0.52)		−0.39 [−0.65, −0.13]
Total	457	0.67	435	1.05		−0.36 [−0.51, −0.22][b]



Reference	CLZ n	CLZ Mean (SD)	TCL n	TCL Mean (SD)	Loss index	WMD [95% CI]
Kamishirado et al., 2002	54	0.16 (0.27)	57	0.42 (0.56)		−0.26 [−0.42, −0.10]
Kozuma et al., 2001	61	0.37 (0.36)	58	0.65 (0.39)		−0.28 [−0.42, −0.14]
Tanabe et al., 2001	63	0.34 (0.26)	55	0.51 (0.28)		−0.17 [−0.27, −0.07]
Park et al., 2000	254	0.46 (0.32)	240	0.52 (0.33)		−0.06 [−0.12, −0.01]
Ochiai et al., 1999	25	0.18 (0.13)	25	0.31 (0.19)		−0.13 [−0.22, −0.04]
Total	457	0.30	435	0.48		−0.16 [−0.24, −0.08][a]



Reference	CLZ n	CLZ Mean (SD)	TCL n	TCL Mean (SD)	Net gain (mm)	WMD [95% CI]
Kozuma et al., 2001	61	1.18 (0.77)	58	0.64 (0.70)		0.54 [0.28, 0.80]
Tanabe et al., 2001	63	1.65 (0.78)	55	1.21 (0.70)		0.44 [0.17, 0.71]
Total	124	1.42	113	0.93		0.49 [0.30, 0.68][a]

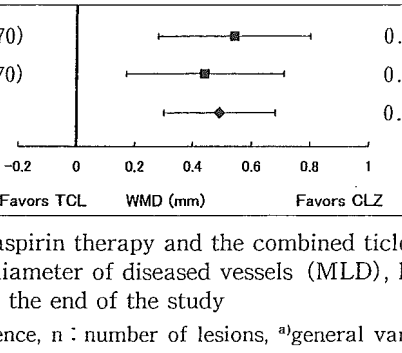


Fig. 2 The difference between the combined cilostazol with aspirin therapy and the combined ticlopidine with aspirin therapy with regard to the change in minimal lumen diameter of diseased vessels (MLD), late loss, loss index, or net gain with quantitative coronary angiography at the end of the study

TCL : ticlopidine, CLZ : cilostazol, WMD : weighted mean difference, n : number of lesions, [a]general variance-based method, [b]DerSimonian-Laird method

Reference	CLZ n/N	TCL n/N	OR [95% CI]
1) Bleeding			
Kamishirado et al., 2002	0/65	0/65	1.00 [0.02, 51.16]
Tanabe et al., 2001	0/54	0/50	0.93 [0.02, 47.58]
Ochiai et al., 1999	0/25	0/25	1.00 [0.02, 52.36]
Total	0/144	0/140	0.98 [0.10, 9.38][a]
2) Intracranial hemorrhage, Cerebral hemorrhage			
Kamishirado et al., 2002	0/65	0/65	1.00 [0.02, 51.16]
Park et al., 2000	0/208	1/201	0.32 [0.01, 7.91]
Total	0/273	1/266	0.50 [0.05, 4.83][a]
3) Vascular complications			
Kamishirado et al., 2002	0/65	1/65	0.33 [0.01, 8.21]
4) Leukopenia, Thrombocytopenia, Neutropenia			
Kamishirado et al., 2002	0/65	1/65	0.33 [0.01, 8.21]
Park et al., 2000	0/208	2/201	0.19 [0.01, 4.01]
Ochiai et al., 1999	0/25	0/25	1.00 [0.02, 52.36]
Total	0/298	3/291	0.36 [0.07, 1.79][a]
5) Skin rash			
Kozuma et al., 2001	1/56	4/58	0.25 [0.03, 2.27]
Park et al., 2000	5/208	0/201	10.89 [0.60, 198.27]
Total	6/264	4/259	1.45 [0.04, 59.25][b]
6) Gastrointestinal disturbance			
Park et al., 2000	8/208	5/201	1.57 [0.50, 4.88]
7) Elevated aminotransferase			
Kamishirado et al., 2002	0/65	7/65	0.06 [0.01, 1.07]
Kozuma et al., 2001	1/56	2/58	0.51 [0.04, 5.78]
Park et al., 2000	0/208	1/201	0.32 [0.01, 7.92]
Ochiai et al., 1999	0/25	0/25	1.00 [0.02, 52.37]
Total	1/354	10/349	0.26 [0.09, 0.77][a]
8) Tachycardia, Palpitation			
Kamishirado et al., 2002	2/65	0/65	5.16 [0.24, 109.56]
Kozuma et al., 2001	1/56	0/58	3.16 [0.13, 79.28]
Total	3/121	0/123	3.42 [0.59, 19.96][a]
Total events	18/1727	24/1694	0.80 [0.47, 1.35][a]

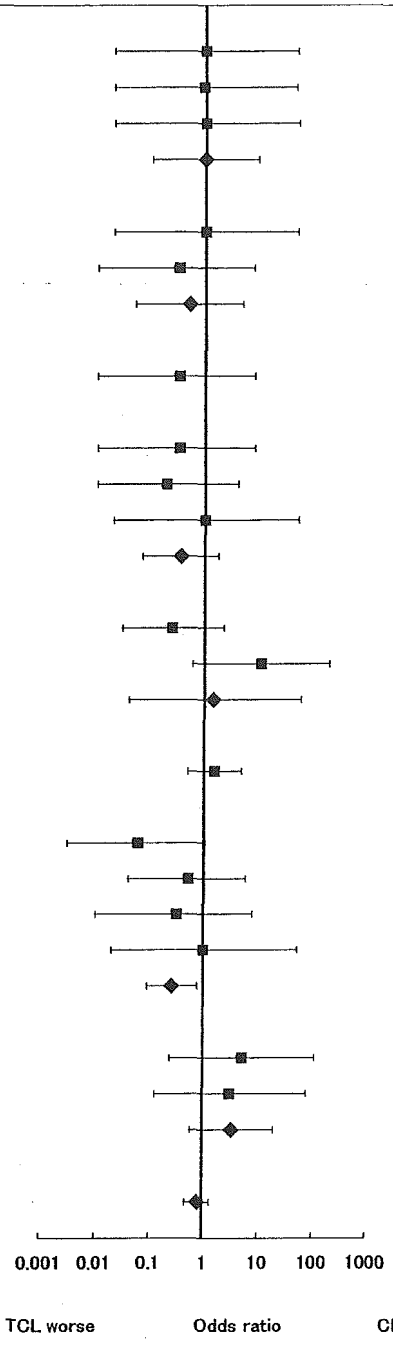


Fig. 3 The odds ratio for the adverse clinical events between the combined ticlopidine with aspirin therapy and combined cilostazol with aspirin therapy

TCL : ticlopidine, CLZ : cilostazol, OR : odds ratio, n : number of patients who reported the event, N : total number of patients, [a]Peto method, [b]DerSimonian-Laird method

vivo[31,32] and has a very slow onset of the effect. In our meta-analysis, we were unable to clearly show that these differences are related to the pharmacological characteristics seen in acute stent thrombosis and subacute stent thrombosis.

We have previously examined the short-term efficacy (1 month) of cilostazol plus aspirin using a meta-analysis and did not find any statistical

difference from that of ticlopidine plus aspirin after elective coronary stenting[18]. On the other hand, our current study suggests that cilostazol's long-term efficacy is superior to that seen for ticlopidine. The reason for this may be due in part to the pharmacological difference between the two drugs as mentioned above.

For adverse clinical events (Fig. 3), our results showed a lower incidence of bleeding, intracranial or cerebral hemorrhage in patients administered cilostazol plus aspirin (0%) or ticlopidine plus aspirin (0%, 0.4%). There were no differences in the incidences of other hematological problems such as leukopenia, thrombocytopenia, or neutropenia between two the therapies. However, ticlopidine plus aspirin (2.9%) therapy has a higher risk for elevated aminotransferase as opposed to cilostazol plus aspirin therapy (0.3%). It is well known that ticlopidine can cause hepatic impairment within the first 2-4 weeks after drug administration initiation. In all published studies that we examined, there were no cases of severe hepatic impairment even though the duration of ticlopidine administration was 1 month in 2 studies, 4 to 6 months in 1 study, and 6 months in 2 studies. It has also been reported that with cilostazol there is the possibility of an increased heart rate and a positive cardiac inotropic effect due to phosphodiesterase III inhibition[33]. Our results found a tendency for a higher incidence of tachycardia or palpitations in patients administered cilostazol (2.5%), but these changes were not statistically significant. In patients with heart failure or with a high risk of arrhythmia, it is not clear as to what the influence of cilostazol may be and published studies do not always exclude such patients. Thus, heart rate or arrhythmia monitoring may be needed for high-risk patients. While our meta-analysis indicated that there was a tendency for a lower incidence of total adverse clinical events in patients with cilostazol (1.0%) versus that seen with ticlopidine (1.4%), there were no statistical significant differences between the therapies. This result suggests that after coronary stenting, cilostazol therapy is almost the same as ticlopidine therapy with regard to safety.

It should be noted that this meta-analysis includes different drug administration and/or follow-up periods, and there is a possibility of publication bias, which could indicate that our results have some limitations. Stent designs also influence long-term angiographic outcome[34,35]. The coil stents (Gianturo-Roubin I and II) have a higher restenosis rate compared with the slotted tube stent (Palmaz-Schatz) or the multicellular stents (MultiLink and NIR). Coil stents are associated with less initial gain because they allow acute recoil and tissue prolapse that is related to the greater amount of open space that is present between the stent struts. In our meta-analysis, the implanted stent designs differed among the studies. We did not take the stent designs into consideration in our study so we might need to carefully re-evaluate our results from this point of view.

Recently, the adjunctive use of glycoprotein (GP) IIb/IIIa inhibitors has been found to be advantageous when administered in combination with intracoronary stent implantation because the GP IIb/IIIa receptors on platelets play a key role in the "final common pathway" of platelet-thrombus formation. Several studies have shown that when used as an adjunct to coronary intervention, intravenous GP IIb/IIIa inhibitors have a beneficial effect with regard to the reduction in restenosis, particularly in patients with unstable angina or in those with high-risk factors[36,37]. Furthermore it has become quite common for the thienopyridine derivative, clopidogrel, to be used in drug-eluting stents in the US and in Europe after coronary stenting. However, this drug has yet to be used in Japan. In studies that have compared clopidogrel and ticlopidine for efficacy/safety after coronary stenting, it has been shown that the clinical efficacy is the same for both drugs and that the safety of clopidogrel is superior to that of ticlopidine[38-40]. Therefore, it will be interesting to see if a comparison of clopidogrel and cilostazol for long-term efficacy yields any differences with regard to use as an adjunctive antiplatelet therapy after coronary stenting.

In conclusion, we reviewed articles published from 1986 until the present and performed a meta-analysis on 5 studies that examined the long-term efficacy and safety of cilostazol and ticlopidine coadministered with aspirin after coronary stenting. The meta-analysis results suggest that a combination therapy of cilostazol and aspirin might be superior to that of ticlopidine and aspirin with

regard to long-term efficacy, particularly as an adjunctive antiplatelet therapy for the prevention of late restenosis.

Acknowledgement

This study was supported in part by Fiscal 2003 Grant-in-Aid (No. 032) for Research on Health Technology Assessment, Ministry of Health, Labor and Welfare of Japan.

References

1) Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med* 1994 ; **331** : 496-501.
2) Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994 ; **331** : 489-95.
3) Smith SC Jr, Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)-executive summary. *Circulation* 2001 ; **103** : 3019-41.
4) Harding SA, Walters DL, Palacios IF, Oesterle SN. Adjunctive pharmacotherapy for coronary stenting. *Curr Opin Cardiol* 2001 ; **16** : 293-9.
5) Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. *Circulation* 1999 ; **100** : 1667-72.
6) Patrono C, Coller B, Dalen JE, FitzGerald GA, Fuster V, Gent M, Hirsh J, Roth G. Platelet-active drugs : the relationships among dose, effectiveness, and side effects. *Chest* 2001 ; **119** : 39 S-63 S.
7) Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 1998 ; **339** : 1665-71.
8) Tanaka T, Ishikawa T, Hagiwara M, Onoda K, Itoh H, Hidaka H. Effects of cilostazol, a selective cAMP phosphodiesterase inhibitor on the contraction of vascular smooth muscle. *Pharmacology* 1988 ; **36** : 313-20.
9) Dawson DL, Cutler BS, Meissner MH, Strandness DE Jr. Cilostazol has beneficial effects in treatment of intermittent claudication : results from a multicenter, randomized, prospective, double-blind trial. *Circulation* 1998 ; **98** : 678-86.
10) Ikeda Y, Kikuchi M, Murakami H, Satoh K, Murata M, Watanabe K, Ando Y. Comparison of the inhibitory effects of cilostazol, acetylsalicylic acid and ticlopidine on platelet functions ex vivo. Randomized, double-blind cross-over study. *Arzneimittelforschung* 1987 ; **37** : 563-6.
11) Take S, Matsutani M, Ueda H, Hamaguchi H, Konishi H, Baba Y, Kawaratani H, Sugiura T, Iwasaka T, Inada M. Effect of cilostazol in preventing restenosis after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1997 ; **79** : 1097-9.
12) Yoshitomi Y, Kojima S, Sugi T, Yano M, Matsumoto Y, Kuramochi M. Antiplatelet treatment with cilostazol after stent implantation. *Heart* 1998 ; **80** : 393-6.
13) Umekawa H, Tanaka T, Kimura Y, Hidaka H. Purification of cyclic adenosine monophosphate phosphodiesterase from human platelets using new-inhibitor sepharose chromatography. *Biochem Pharmacol* 1984 ; **33** : 3339-44.
14) Kimura Y, Tani T, Kanbe T, Watanabe K. Effect of cilostazol on platelet aggregation and experimental thrombosis. *Arzneimittelforschung* 1985 ; **35** : 1144-9.
15) El-Beyrouty C, Spinler SA. Cilostazol for prevention of thrombosis and restenosis after intracoronary stenting. *Ann Pharmacother* 2001 ; **35** : 1108-13.
16) Kunishima T, Musha H, Eto F, Iwasaki T, Nagashima J, Masui Y, So T, Nakamura T, Oohama N, Murayama M. A randomized trial of aspirin versus cilostazol therapy after successful coronary stent implantation. *Clin Ther* 1997 ; **19** : 1058-66.
17) Yamasaki M, Hara K, Ikari Y, et al. Effects of cilostazol on late lumen loss after Palmaz-Schatz stent implantation. *Cathet Cardiovasc Diagn* 1998 ; **44** : 387-91.
18) Hashiguchi M, Ohno K, Nakazawa R, Kishino S, Mochizuki M, Shiga T. Comparison of cilostazol and ticlopidine for one-month effectiveness and safety after elective coronary stenting. *Cardiovasc Drugs Ther* 2004 ; **18** : 211-7.
19) Morizane T. *EBM Upgrade for Physicians*. Tokyo : Igakushoin, 2002 : 131-7 (in Japanese).
20) Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomized studies of health care interventions. *J Epidemiol Community Health* 1998 ; **52** : 377-84.
21) Cho MK, Bero LA. Instruments for assessing the quality of drug studies published in the medical literature. *JAMA* 1994 ; **272** : 101-4.
22) Kamishirado H, Inoue T, Mizoguchi K, Uchida T, Nakata T, Sakuma M, Takayanagi K, Morooka S. Randomized comparison of cilostazol versus ticlopidine hydrochloride for antiplatelet therapy after coronary stent implantation for prevention of late restenosis. *Am Heart J* 2002 ; **144** : 303-8.
23) Kozuma K, Hara K, Yamasaki M, Morino Y, Ayabe S, Kuroda Y, Tanabe K, Ikari Y, Tamura T. Effects of cilostazol on late lumen loss and repeat revascularization after Palmaz-Schatz coronary stent implantation. *Am Heart J* 2001 ; **141** : 124-30.
24) Park SW, Lee CW, Kim HS, Lee NH, Nah DY, Hong MK, Kim JJ, Park SJ. Effects of cilostazol on angiographic restenosis after coronary stent placement. *Am J Cardiol* 2000 ; **86** : 499-503.
25) Ochiai M, Eto K, Takeshita S, Yokoyama N, Oshima A, Kondo K, Sato T, Isshiki T. Impact of cilostazol on clinical and angiographic outcome after primary stenting for acute myocardial infarction. *Am J Cardiol* 1999 ; **84** : 1074-6, A 6, A 9.
26) Tanabe Y, Ito E, Nakagawa I, Suzuki K. Effect of cilostazol on restenosis after coronary angioplasty and stenting in comparison to conventional coronary artery stenting with ticlopidine. *Int J Cardiol* 2001 ; **78** : 285-91.

27) Takahashi S, Oida K, Fujiwara R, Maeda H, Hayashi S, Takai H, Tamai T, Nakai T, Miyabo S. Effect of cilostazol, a cyclic AMP phosphodiesterase inhibitor, on the proliferation of rat aortic smooth muscle cells in culture. *J Cardiovasc Pharmacol* 1992 ; **20** : 900-6.
28) Kubota Y, Kichikawa K, Uchida H, et al. Pharmacologic treatment of intimal hyperplasia after metallic stent placement in the peripheral arteries. An experimental study. *Invest Radiol* 1995 ; **30** : 532-7.
29) Pan X, Arauz E, Krzanowski JJ, Fitzpatrick DF, Polson JB. Synergistic interactions between selective pharmacological inhibitors of phosphodiesterase isozyme families PDE III and PDE IV to attenuate proliferation of rat vascular smooth muscle cells. *Biochem Pharmacol* 1994 ; **48** : 827-35.
30) Kayanoki Y, Che W, Kawata S, Matsuzawa Y, Higashiyama S, Taniguchi N. The effect of cilostazol, a cyclic nucleotide phosphodiesterase III inhibitor, on heparin-binding EGF-like growth factor expression in macrophages and vascular smooth muscle cells. *Biochem Biophys Res Commun* 1997 ; **238** : 478-81.
31) Okuda Y, Kimura Y, Yamashita K. Cilostazol. *Cardiovasc Drug Rev* 1993 ; **11** : 451-65.
32) Defreyn G, Bernat A, Delebassee D, Maffrand JP. Pharmacology of ticlopidine : a review. *Semin Thromb Hemost* 1989 ; **15** : 159-66.
33) Harker A, Bruno JJ. Ticlopidine's mechanism on action on human platelets. Hass K, Easton JD (Eds). *Ticlopidine, Platelets, and Vascular Disease*. New York : Springer-Verlag, 1993 : 41-59.
34) Cone J, Wang S, Tandon N, Fong M, Sun B, Sakurai K, Yoshitake M, Kambayashi J, Liu Y. Comparison of the effects of cilostazol and milrinone on intracellular cAMP levels and cellular function in platelets and cardiac cells. *J Cardiovasc Pharmacol* 1999 ; **34** : 497-504.
35) Escaned J, Goicolea J, Alfonso F, Perez-Vizcayno MJ, Hernandez R, Fernandez-Ortiz A, Banuelos C, Macaya C. Propensity and mechanisms of restenosis in different coronary stent designs : complementary value of the analysis of the luminal gain-loss relationship. *J Am Coll Cardiol* 1999 ; **34** : 1490-7.
36) Lansky AJ, Roubin GS, O'Shaughnessy CD, et al. Randomized comparison of GR-II stent and Palmaz-Schatz stent for elective treatment of coronary stenoses. *Circulation* 2000 ; **102** : 1364-8.
37) Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. *Lancet* 1999 ; **353** : 227-31.
38) De Luca G, Suryapranata H, van't Hof AW, Ottervanger JP, Hoorntje JC, Gosselink AT, Dambrink JH, Zijlstra F, de Boer MJ. Comparison between ticlopidine and clopidogrel in patients with ST-segment elevation myocardial infarction treated with coronary stenting. *Thromb Haemost.* 2004 ; **91** : 1084-9.
39) Berger PB, Bell MR, Rihal CS, et al. Clopidogrel versus ticlopidine after intracoronary stent placement. *J Am Coll Cardiol.* 1999 ; **34** : 1891-4.
40) Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators FT. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation.* 2000 ; **102** : 624-9.

Surg Today (2005) 35:553–560
DOI 10.1007/s00595-005-2998-3

SURGERY TODAY

Early Versus Delayed Cholecystectomy for Acute Cholecystitis: A Meta-analysis of Randomized Controlled Trials

SATORU SHIKATA[1], YOSHINORI NOGUCHI[2], and TSUGUYA FUKUI[3]

[1]Department of Surgery, Division of Digestive Surgery, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan
[2]Division of General Internal Medicine, Department of Medicine, Fujita Health University School of Medicine, Aichi, Japan
[3]Department of General Medicine and Clinical Epidemiology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

Abstract

Purpose. We performed a meta-analysis of randomized controlled trials to determine the optimal timing of laparoscopic cholecystectomy and open cholecystectomy for acute cholecystitis.

Methods. We retrieved randomized controlled trials (RCTs) that compared early with delayed cholecystectomy for acute cholecystitis by systematically searching Medline and the Cochrane Library for studies published between 1966 and 2003. The outcomes of primary interest were mortality and morbidity.

Results. The ten trials we analyzed comprised 1014 subjects; 534 were assigned to the early group and 480 assigned to the delayed group. The combined risk difference of mortality appeared to favor open cholecystectomy in the early period (risk difference, −0.02; 95% confidence interval, −0.44 to −0.00), but no differences were found among laparoscopic procedures or among all procedures. The combined risk difference of morbidity showed no differences between the open and laparoscopic procedures. The combined risk difference of the rate of conversion to open surgery showed no differences in the included laparoscopic studies; however, the combined total hospital stay was significantly shorter in the early group than in the delayed group.

Conclusions. There is no advantage to delaying cholecystectomy for acute cholecystitis on the basis of outcomes in mortality, morbidity, rate of conversion to open surgery, and mean hospital stay. Thus, early cholecystectomy should be performed for patients with acute cholecystitis.

Kew words Meta-analysis · Cholecystectomy · Early · Delay

Reprint requests to: T. Fukui
Received: March 22, 2004 / Accepted: November 16, 2004

Introduction

Open cholecystectomy was the standard treatment for acute cholecystitis for several decades. When laparoscopic cholecystectomy was first introduced in 1987, acute cholecystitis was a contraindication for this operation;[1–3] however, increased experience with this condition has led to laparoscopic cholecystectomy being equivalent to, or better than, open cholecystectomy for its treatment.[4] The specific purpose and timing of both open and laparoscopic cholecystectomy in the treatment of acute cholecystitis is a subject of some debate. Many clinicians still believe that inflammation, edema, and adhesions, which are commonly associated with cholecystectomy, make early surgery unsafe.

The benefits of both open and laparoscopic cholecystectomy have been substantiated by several randomized controlled trials (RCTs) showing that the early-operation strategy is associated with a shorter hospital stay without added morbidity.[5–11] However, other studies show an association between early procedures and an increase in morbidity.[12–14] Although several review articles and RCTs have addressed this issue, no meta-analyses of RCTs have been published.[5–16] In light of this, we performed a meta-analysis of RCTs to determine the optimal timing of laparoscopic cholecystectomy and open cholecystectomy for acute cholecystitis.

Methods

Search strategy

Retrieval of RCTs was based on the Cochrane Central Register of Controlled Trials (Cochrane Library, until issue 4, July 2003) and Medline (January 1966 to September 2003). The following search terms were used: "cholecystitis," "cholecystectomy," "early," and

"delayed." We supplemented electronic searches by hand searching reference lists and reviews. Trials in any language were taken into account.

Inclusion and Exclusion Criteria

This meta-analysis included studies that met the following four criteria: study design (randomized controlled trial), main purpose (comparing the effectiveness of early with delayed cholecystectomy), target population (patients with acute cholecystitis), and availability of mortality and morbidity data. We excluded studies that used cholecystectomy for cancer and those that were not RCTs. Each author first decided independently which reports should be included in the analysis. Then, any disagreement was settled by consensus among all investigators.

Data Collection

Data were collected independently by two investigators (SS and YN), with any disagreement resolved by a third reviewer (TF).

Outcome Measures

The outcomes of primary interest were mortality and morbidity related to cholecystectomy. Secondary outcomes were the rate of conversion to open surgery, hospital stay, operation time, and bleeding.

Quality Assessment of Primary Studies

We evaluated the quality of primary studies as described by Jadad et al.[17] This method assesses the description of randomization, appropriateness of randomization, description of double blinding, appropriateness of double blinding, and description of withdrawals or dropouts on a five-point scale. The minimum number of points possible was 0 and the maximum, 5.

Sensitivity Analysis

We performed a sensitivity analysis by excluding low-quality studies, defined as studies receiving a score of 2 or less on the Jadad scale, and assessed the impact of study quality.

Assessment of Publication Bias

The potential for publication bias was examined by the funnel plot method,[18] and the significance of differences was evaluated by the method of Begg and Mazumdar[19] and Egger et al.[20] A P value of publication bias less than 0.10 was considered significant.

Statistical Analysis

We calculated the risk difference for the outcomes of the trials and weighted pooled estimates for the data. The fixed-effect model weighted by the Mantel-Haenszel method was used for pooling the risk differences,[21] followed by a test of homogeneity. Homogeneity among studies was assessed using the χ-squared test (Q statistics).[22] P value of homogeneity less than 0.10 was considered significant. If the hypothesis of homogeneity was rejected, than the random-effect model using the DerSimonian-Laird method was used.[23] All statistical analyses were performed with the aid of STATA statistical software.[24] Results are expressed as means with 95% confidence intervals (CIs), unless otherwise indicated. A P value of less than 0.05 was considered significant.

Results

Trial Flow

Figure 1 shows the summary profile of the search. The database search yielded 141 articles, and the manual search of bibliographies in these articles yielded no further articles. Of the 141 articles selected, 14 met the inclusion criteria, but 4 of them were excluded because of multiple publication. Thus, the final analysis consisted of ten studies: four of laparoscopic cholecystectomy and six of open cholecystectomy. Our agreement on the selection of relevant articles was 100%.

Study Characteristics

The ten included trials comprised 1014 subjects. We assigned 534 to the early procedure group (early group) and 480 to the delayed procedure group (delayed group). The four studies on laparoscopic procedures (laparoscopic studies) comprised 363 subjects; 193 were assigned to the early group and 170 to the delayed group. The six studies on open procedures (open studies) comprised 651 subjects; 341 were assigned to the early group and 310 to the delayed group. Table 1 shows the baseline characteristics of the subjects in the included studies. The average age in the study by Chandler et al.,[5] 36/39 (early/delayed), was younger than that in the other studies, and the proportion of male subjects in the study by McArthur et al.,[13] 7%/18% (early/delayed), was much lower than in the other studies.

All primary studies met the inclusion criteria of patients with acute cholecystitis, but exclusion criteria and definitions of the terms "acute cholecystitis," "early operation," and "delayed operation" differed among the studies (Table 2).